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THE RELATIONS OF SCAPULAR TYPES TO PROBLEMS OF HUMAN HEREDITY, LONGEVITY, MORBIDITY AND ADAPTABILITY IN GENERAL*

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ST. LOUIS

"Heredity is a convenient term for the genetic relation between successive generations."—"Heredity determines the individual life."—J. Arthur Thomson.

"Life is short and the art long; the occasion fleeting; experience fallacious and judgment difficult."—"It is the business of the physician to know, in the first place, things similar and things dissimilar." Thus spoke the Father of Medicine.

Human experience teaches that like tends to beget like in the propagation of plants and animals. Yet no two are exactly alike. Resemblances, similarities and differences are found among individuals of any species, but Nature has produced no duplicates. Each individual is truly the first and last of its particular kind. However close may be the kinship of individual A and individual B, they are never equal in their natural endowments. A is always more or less competent than B in structure and function; always more or less competent than B in capacities for adaptation. The relations of structure, function and environment are so close that we cannot think of the one without the others. Structures and functions, in their combined and reciprocal relations, make up the individual organism, and it is with them that it struggles for existence, adapts itself excellently, well or poorly to an ever varying environment and finally perishes. Because no two human beings are alike; because they differ in natural endowments and consequently in structures, functions, acquirements and total makeup; because they differ in their innate capacities for adaptation, the individual is a fundamental and universal problem. Every day observations reveal glaring structural and functional differences, similarities and inequalities in individuals of any species, and this is especially true of the human. As physicians, we do not always realize that such of these as are inherited may be utilized as conditional indices of a person's adaptability, of his capacities for health or disease, or even of his

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many or few years of life. Among the inherited differences, similarities and inequalities abounding in the structures of the human species, and among those readily recognizable in the living are certain variations of the shoulder-blade.

The scapula is one of the distinctive bones of the body, is composed of many varying characteristics and is of unusual functional importance. Prior to investigations, beginning in 1906, it had received comparatively little consideration by anatomists, anthropologists and clinicians. Nevertheless, its general form and some of its special features had been described; its relation with muscles and contiguous bones investigated; its range in variation emphasized, Broca,[1] Mivart,[2] Turner,[3] and Dwight;[4] some racial and sex differences pointed out, Broca,[1] Livon,[5] Dorsey[6] and Flower;[7] its comparative anatomy considered, Mivart,[2] Turner,[3] Dwight,[4] Ranke[8] and Schück;[9] some of its indices established, Broca[1] and Martin,[10] and its ossification and growth from fetal to adult life described. But a scapula was still a scapula. It was merely one among many bones of the body, and aside from its importance to proper function of the shoulder girdle and upper extremities, it had attained no particular significance.

Prior to my investigations, no one, so far as I know, had made comparative studies of the many and varying characteristics of human scapulae and classified them. It is the purpose of this paper to recall observations leading to the classification of human scapulae into readily recognizable types, to mention the scope, and to summarize some of the results of those investigations fundamental to an appreciation of the relations of scapular types to problems of human heredity, longevity, morbidity and adaptability in general.

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On Sept. 18, 1906, while making a routine physical examination in the neurological clinic of the St. Louis University School of Medicine, of A. R., a boy, aged 7 years, I was impressed with the peculiar contour of the vertebral borders of his shoulder-blades. Each vertebral border was distinctly concave (the right more than the left) from the mergence of the spine of the scapula with the vertebral border, to a point slightly above the inferior angle of the bone. These borders and the inferior angles stood out prominently, like wings. The vertebral borders were unusually far apart and their general course paralleled the spinal axis.

Fig. 1.—The R1 family, Dec. 2, 1909, approximately three years after initial observation. Father 46, mother 42, A. 10, C. 8, and L., 5½ years of age, respectively. A similar view of the children 10 years later is shown in Figure 4.

The boy's neck appeared unusually long. His shoulders were hanging, drooping downward and forward, and the right was lower than the left. The thorax was well formed, though shallow and somewhat narrowed about the lower costosternal junction. The clavicles took a distinctly horizontal course, the abdomen was unduly prominent about its lower half and the body attitudes were those of extreme sluggishness. His stature and weight were much less than the average, and his muscle development was meager without evident atrophy. He was able to assume normal attitudes, to elevate and approximate his shoulder blades in a proper manner and to execute all movements with strength propor-

tionate to muscular development. His mother, aged 39, disclosed vertebral borders more concave than those of the patient and poor general developement; whereas his father, aged 43, disclosed convex vertebral borders and good general development. The younger children, a boy, aged 5 years, and a girl aged 3 years, disclosed concave vertebral borders, and in general makeup the three children resembled the mother rather than the father (Fig. 1).

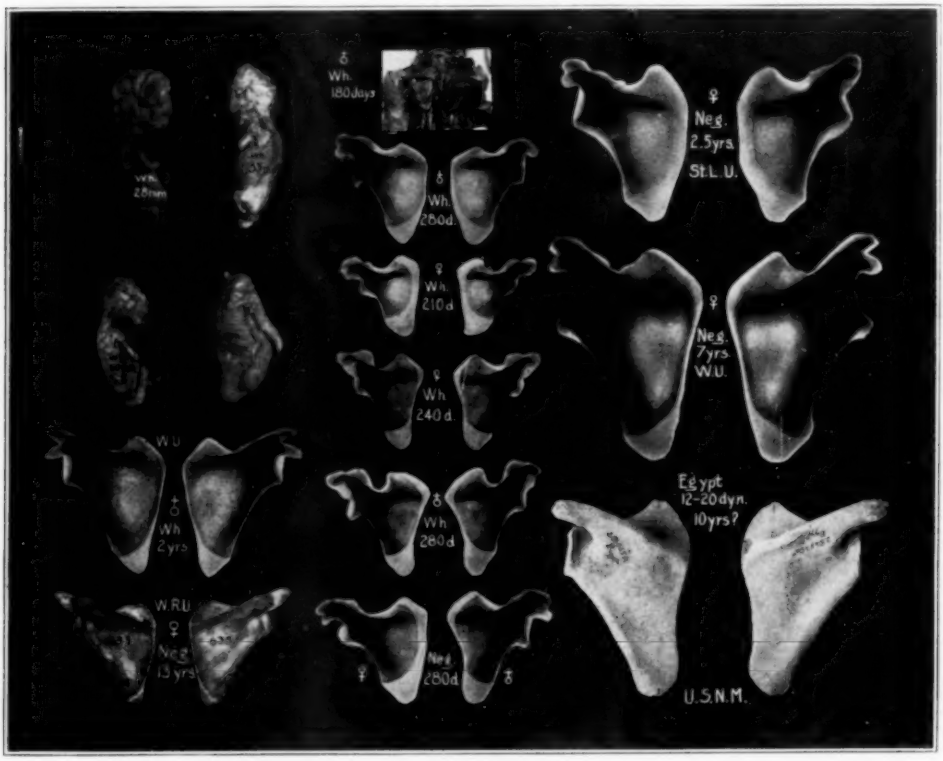

Fig. 2.—Convex, straight and concave scapular types from approximately tenth fetal week to thirteenth year of life. Note the varying relation of bone to cartilage in the roentgen-ray figures and in those marked 633, and the loss of cartilaginous glenoid, acromion, vertebral border and inferior angle regions in the Egyptian. Compare with Figure 3.

CLASSIFICATION

Since the vertebral border of the human scapula had been described, and usually pictured as having a more or less convex outline similar to that found in the father of the R1 family, the finding of concave ver-

tebral borders in the mother and the three children, associated with rather poor general development, led to further observations on scapular-vertebral-border formation on living subjects and to intimate studies of skeletal and fetal scapulae. Observations on living subjects soon revealed the existence of a limited range in variation of scapular vertebral borders, from markedly convex to markedly concave. In some persons I found markedly, in some moderately, in some slightly concave; in some markedly, moderately or slightly convex; in others vertebral borders neither convex nor concave but intermediate in contour, seemingly straight or nearly so. Comparative studies of living and similar studies of skeletal and fetal material have led to the classification of human scapulae into convex, straight and concave types (Figs. 2, 3 and 5).

The classification is based on the relation of a straight line to the greater portion of the vertebral border below the scapular spine, but fundamentally it is based on a combination of the anatomic and architectural features peculiar to each type. In my first communication [11] in 1910, I pointed out five or more features common to straight and concave types. That study was based on only 198 mature skeletal scapulae, of which 61 per cent. were convex, 26 per cent. straight and 13 per cent. concave. In a recent comparative study of 1,219 mature bones, it has been clearly shown that the concave and the straight have twelve or more features in common, and, therefore, constitute a variant type con-

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11. Graves, W. W.: The Scaphoid Scapula: a Frequent Anomaly in Development of Hereditary, Clinical and Anatomical Significance, M. Rec. **78**: 861-873, 1910; The Clinical Recognition of the Scaphoid Type of Scapula and Some of Its Correlations, J. A. M. A. **55**:12-17 (July) 1910; J. Missouri M. A. **7**: (Dec.) 1910; Some Remarks on the Scaphoid Scapula and Its Syndrome, Tr. Nat. Assn. Study Epilepsy **8**:56 (June 16) 1911; The Scaphoid Scapula Syndrome; Its Connection with Syphilis in the Ascendants, Interstate M. J. **18**: 109-116, 1911; transl. Deutsch. Ztschr. f. Nervenh. **41**:247-257, 1911; Scapula scaphoidaea eine häufig vorkommende Anomalie des Schulterblattes, Ihr Zusammenhang mit Syphilis in der Aszendenz, Med. Klin. **8**:208-301, 1911; Einige Bemerkungen über die Skaphoidskapula und ihre Begleiterscheinungen (Translation of Ref. No. 3 by V. Kollert) Wien. klin. Wchnschr. **25**:245-258, 1912; Remarks on the Scaphoid Scapula and Its Syndrome; the Connection with Syphilis in the Ascendants, J. Cutan. Dis. incl. Syph. **31**:241-245, 1913; The Age Incidence of the Scaphoid Type of Scapula: Its Bearing Upon Problems of Racial Morbidity, in Contributions to Med. & Biol. Research, dedicated to Sir William Osler, Vol. 1, New York, Paul B. Hoeber, 1919, pp. 525-532; An Appeal for Embryos and Foetuses, J. A. M. A. **73**:1788 (Dec. 6) 1919; Discussion: The Scaphoid Type of Scapula, Am. J. Syphilis **4**:478, 1920; The Types of Scapulae: A Comparative Study of Some Correlated Characters in Human Scapulae, Am. J. Phys. Anthropol. **4**:111, 1921; Observations on Age Changes in the Scapula: A Preliminary Note, Am. J. Phys. Anthropol. **5**:21, 1922; The Age Incidence of Scapular Types: Its Possible Relation to Longevity, Trans. Am. Assn. Life Ins. Med. Directors, 1923.

trasting vividly with the convex.[12] These comparative studies have justified combining the straight and concave forms and designating them the *scaphoid type* (Fig. 5). Further justification was found in the fact that persons in whom the vertebral border was classified straight often disclosed deviating characteristics in total makeup similar to, although, as a rule, less marked than in those in whom it was found to be concave.

Because the scaphoid (concave or straight) was found with relative frequency in all periods of life; because more or less convexity of the vertebral border had been considered by anatomists a characteristic of the so-called "normal" or "average" scapula in man; and because mammalian families below man, as a rule, disclosed more or less convex scapular vertebral borders, I formerly considered the scaphoid type an anomaly in development, and I have in my writings repeatedly referred to it as such.[11] Further investigations of living and skeletal material of man and of vertebrate skeletal material in general, and a better appreciation of the range of variation in the structures and functions in man's total makeup, have convinced me that it is erroneous to consider the scaphoid type (concave or straight) an anomaly. It would be equally valid to consider the convex an anomaly for the reason that each scapular type (convex, straight or concave) is fundamentally a combination of morphologic and architectural features peculiar to human scapulae. Therefore, it is erroneous to consider any one of the three types as the "normal" or the "average" type. Further reasons for this conclusion will presently become obvious.

THE RELATIONS OF SCAPULAR TYPES TO PROBLEMS OF HEREDITY: THEIR PRIMAL OR GERM-PLASM ORIGIN

Observations on living and skeletal material from birth to old age show the presence of convex, straight and concave scapular types in all period of life in varying degrees and percentages.

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12. The chief characters common to the straight and concave types contrasting with similar characters in the convex are as follows: (1) Thickness of the vertebral border; (2) "vertebral-border buds" or processes varying in location, size and number; (3) "vertebral-border remnants," meaning a part of the vertebral-border system (lips and intermediary surface) morphologically more or less complete; (4) three scapular indices: Broca's scapular and infraspinous indices and Hrdlička's index; (5) the degree of angle formed by the long scapular axis with the general direction of the scapular spine ("long scapular axis-spinal angle"); (6) the relation of the vertebral border below the scapular spine to a straight edge; (7) the relation of the inferior border to a horizontal, or to a vertical when the long scapular axis is vertical; (8) the relation of the teres major process to axillary border; (9) the relation of the long axis of glenoid to long scapular axis; (10) the character of the inferior-angle region; (11) the densities of the bones to transmitted light; (12) the densities of the bones to the roentgen-ray; (13) muscle markings of bones in approximately the same age periods; (14) average weight of bones having similar long axis measurements in approximately the same age periods.

Dissections of fetal scapulae in approximately the tenth week of development (when the human scapula is mainly cartilaginous) and onward in prenatal life, show convex, straight and concave types (Fig. 2.)

Observations on the living in our population, regardless of age, sex, race, stock, environment, occupation, social level, health, disease, type or build, show the presence of convex, straight and concave scapular types in varying degrees and percentages.

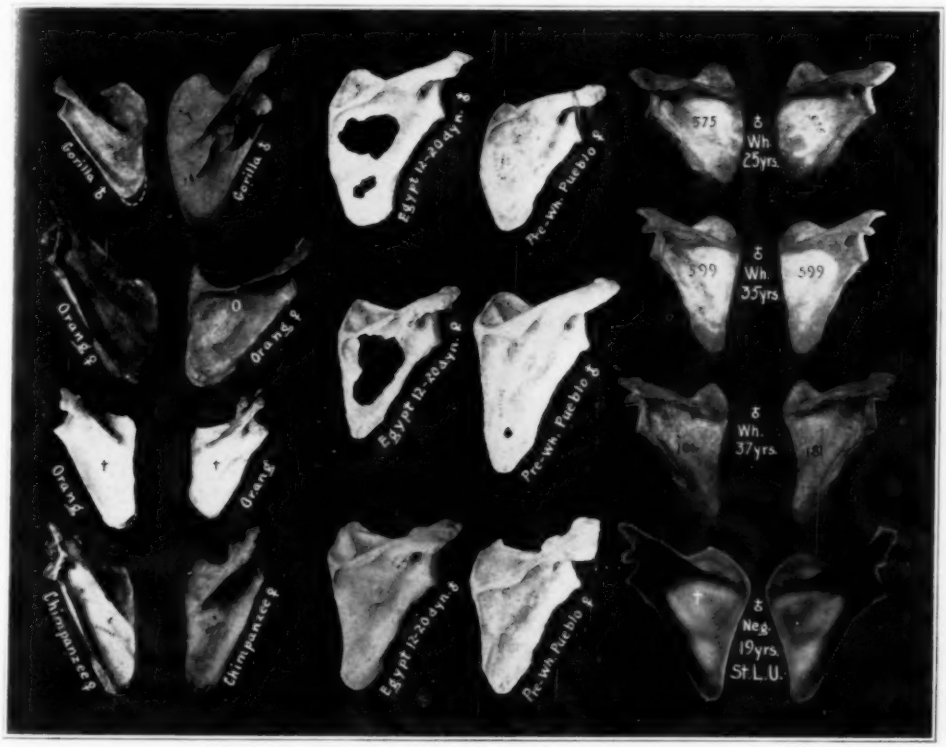

Fig. 3.—Mature scapular types in apes and in ancient and modern man. Ossification is complete in all, except in one gorilla and in those marked † and in orang-utan marked O. Immature gorilla, orang-utan and human scapulae show similar morphology. (Compare Figs. 2 and 3). Cartilaginous vertebral border of scapula in right lower corner was removed before being roentgenogrammed. (The scapulae of apes, Egyptians and American-Indians were photographed by permission of Drs. A. Hrdlička and G. S. Miller, Jr. [U. S. National Museum], and those numbered 633, 575, 599 and 181 were photographed by Prof. T. W. Todd [Hamann Mus. W. R. Med. School]).

Observations on approximately 3,500 skeletal scapulae representing the several races of man, beginning with modern and going back as far as pre-dynastic Egyptian, show the presence of convex, straight and concave types in all races thus far investigated. Similar types are also found in several mammalian families below man, and particularly in the orang-utan, gorilla and chimpanzee [11] (Fig. 3).

The number and percentages of convex, straight and concave scapular types, from mixed-stock dissecting room material in 1,219 mature bones, whose bearers ranged in years from under 25 to over 96, with an average age of approximately 50 years were found to be as follows:

	Mature Bones	Percentages
Convex	663	54.3
Straight	320	26.2
Concave	236	19.5

The scapulae of ancient man thus far found in sufficient numbers (unknown average age), when classified, yielded the following numbers and percentages:

Twelfth to Twentieth Dynasty Egyptians (U. S. National Museum)[11]

	Mature Bones	Percentages
Convex	20	44.4
Straight	13	28.8
Concave	12	26.8

Pre-Columbian Peruvian Indians (U. S. National Museum)[11]

	Mature Bones	Percentages
Convex	32	66.6
Straight	11	22.9
Concave	5	10.5

Pre-White Pueblo Indians (U. S. National Museum)[11]

	Mature Bones	Percentages
Convex	77	69.3
Straight	22	19.8
Concave	12	10.9

The presence and percentages of the three types in the remains of ancient and modern man; the finding of identical scapular types in prenatal and postnatal life periods, regardless of sex, race and environmental influences; and the finding of similar types in mammals below man, justify the inferences that all races of man at all times have shown similar variations and types, and that the origin of scapular types in man is primal.

THE INHERITANCE OF SCAPULAR TYPES—"NORMAL" AND "ALTERED"

Positive proof of the primal or germ-plasm origin of scapular types is found in comparative studies of parents and progeny. Such origin was clearly indicated in the observations on the R 1 family, and one need only examine the members of his own family to find indubitable evidence of the fact. Comparative studies of as many members as were

accessible in approximately 1,000 families, representing two, three, four and five generations have shown that the resultant scapular types in the progeny were usually dependent on scapular type matings, i. e., the kind of scapular types possessed by parents. These studies have led me to the conclusion that in *no single recognizable morphologic or functional trait or characteristic of human inheritance, with the exception of definite racial characteristics, do the progeny more frequently and more closely resemble each other and one or both parents than in shoulder-blade types.* Under "normal" circumstances the transmission of scapular types, with but few exceptions is found to be as follows: Similar scapular-type matings (convex + convex, or concave + concave) produce similar scapular types in the progeny; dissimilar scapular-type matings (convex + concave) produce the scaphoid type in varying degrees (from concave to straight) in the progeny. The chief exceptions to these findings thus far noted appear to be due to occasional examples of atavism, or to the occasional presence of some disease or other poison factor in both parents. When only one child in a family of several children discloses a scapular type differing from that found in both parents, such a finding is construed as an example of atavism. When most, or all of the several children disclose types differing from those possessed by both parents, such findings are construed as evidence of altered scapular type inheritance. Considering the possible degrees of convexity or concavity (variations) in vertebral-border-contour formation in scapular type matings, the resultant scapular types in the progeny seem to be examples of *blending* rather than of *mendelian* inheritance, but my investigations are wholly insufficient to warrant at this time a definite conclusion one way or the other. Nevertheless, through family studies indubitable proof of the foregoing inference, i. e., the primal, or germ-plasm origin of scapular types, has been found. This inference, it will be recalled, was based on the following ascertained and readily demonstrable facts: (1) the presence and relative percentages of each scapular type in the remains of ancient and modern man; (2) the presence of similar scapular types in some mammals below man; (3) their presence in all prenatal and postnatal periods from the tenth fetal week onward; and (4) their presence in varying degrees and percentages in all social levels represented in our population, regardless of age, sex, race, type build or environmental influences: therefore, the finding of any scapular type (convex, straight or cancave) in any person justifies the conclusion that it is innate with him, normal to him —a morphologic expression of his germ-plasm inheritance—even though the germ-plasm from which he developed may have been altered by disease toxins and possibly by some other poisons.

My observations thus far show that the frequency of "altered" is practically negligible when compared with the frequency of "normal"

(unaltered) germ-plasm inheritance in reference to scapular types. I have found thus far no disease other than syphilis or other poison, capable of altering scapular type inheritance, but Reye [13] believes that alcoholism and tuberculosis in parents with convex types may have similar effects. However, he did not fully appreciate the necessity of examining both parents, as well as all of the progeny.

Several workers, notably Draeseke,[14] Reye,[13] Cunningham,[15] Warburg,[16] Brückner,[17] Hosteing,[18] Thielke,[19] Balli,[20] Ravold,[21] Lance [22] and many others have construed my writings to mean that syphilis is the only cause of the scaphoid and is, therefore, a sign of congenital syphilis, or of syphilis in the ascendants. No assumptions could be further from the truth,[11] but there is some foundation for them in the fact that I at one time erroneously accepted the convex as the "normal" or "average" type in man and that, for good reasons, repeatedly emphasized syphilis as one factor that may alter scapular type inheritance in the progeny of convex-scapular-type matings.[11] Whether this disease in both parents having convex scapulae, has altered scapular type inheritance in their progeny can be determined only by comparative anthropometric and clinical studies. Such studies have not been recorded by any of the authors just mentioned, except Reye,[13] and his findings are in accord with mine in showing that altered scapular type inheritance is present in the progeny of some syphilitic parents having convex scapular types, but by no means in the progeny of all such parents. Whether a scapular type in a given individual is part of his "normal" or "altered" inheritance can be determined only by comparing him with the other members of his generation, with his parents and, when possible, with his more remote

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ascendants. We do not yet know the frequency with which syphilis or other poisons do or may alter human parental germ-plasm, but the finding of altered scapular type inheritance in the progeny of some syphilized convex scapular type matings appears to be the first conclusive evidence of the fact.[23]

BIOLOGIC STANDARDS: CONDITIONAL MORPHOLOGIC INDICES: THE RELATIONS OF SCAPULAR TYPES TO PROBLEMS OF ADAPTABILITY IN GENERAL

Every day observations reveal biologic inequalities—inherited variations in structures, functions, total makeup and fitness in human beings—but we have found as yet no standard better than the ascendants and collaterals for measuring such inequalities, nor are we likely to find such. Since scapular types show unusually frequent relations to heredity, they are useful conditional indices of the constitution of man. They are not, however, standards with which we may measure man, any of his structures, any of his functions. A particular scapular type is only one part of an individual's inheritance; hence it is a conditional, not an absolute, index. The worth of any inherited feature as an index can only be determined by considering the number and degree of inherited variations coexistent with it. The usefulness of scapular types as conditional morphologic indices is indicated by their relations to the attributes of an ideal in total makeup and adaptation. We constantly define and utilize the attributes of such an ideal when we so readily classify human beings as "weak" or "strong" and as "excellent," "good" or "poor" types. The attributes of a practical ideal appear to be good degrees of symmetry, proportion and harmony in total makeup and good degrees of adaptation in structures and functions: the same in human beings as in all living things. Now a consideration of these attributes in our study of the whole individual will usually enable us to discern his nearness to, or remoteness from, such an ideal. Human beings possessing

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23. Clinical observations of many physicians and the original investigations of E. Fournier (Syphilis Hereditaria Tarda, Ger. Trans. by K. Reis, 1908), in reference to the frequent occurrence of deviations in the progeny of syphilitic parentage and the original studies of Paul on "The Products of Conception in Lead Workers" (Arch. gén. de méd. **15**:513-534, 1860), clearly indicate the harmful effects of both syphilis and lead on human germ-plasm. That the germplasm of lower forms can be altered by chemicals and other agents is conclusively shown in the results of investigations in recent years by many workers and among these may be mentioned Bardeen (J. Exp. Zool. **4**:1-44, 1907); Tower (Pub. Carnegie Inst., 1906); Watson (Brit. M. J., Oct. 28, 1905); MacDougal (Botan. Gaz. **51**:241-257); Stockard and Co-Workers (J. Exper. Zool. **26**:119-226, 1918; Proc. Am. Phil. Soc. **62**:31, 1923); Cole & Bachhuber (Proc. Soc. Exper. Biol. & Med. **12**:24-29); Pearl (J. Exper. Zool. **22**, 1917, part 1, 125-164; part 2, 165-186; part 3, 241-310); Weller (J. Med. Res. N. S. **28**: 271, 1915).

these attributes to a good degree disclose "the healthy mind in the healthy body," and they are readily recognized as belonging to the better types of the race. They seem to be endowed with such capacities that they adapt themselves well to varying environment, resist disease, survive and often attain long life. As physicians we seldom come in contact in a professional way with these types, with the "near to the ideal" in total make up and adaptation. Our medical and social problems are mainly with those types disclosing definite asymmetry, disproportion, disharmony and more or less defective adaptation of structures and functions. It is usually in such types that the favorable soil (capacities) for the development of various and manifold disease processes are found. It is mainly these types that fill to overflowing our penitentiaries, houses of correction, special colonies, alms houses, hospitals and offices. Human experience teaches: (1) that many of such types are lacking in capacities for adaptation in general; (2) that their resistance in the broadest sense is often poor; and (3) that many of them succumb early in life and proportionately few of them attain even moderately long life.

My comparative studies of individuals, of members of families and of groups have shown that it is in those who are found to be innately more or less remote from an easily recognized ideal in total makeup and adaptation, the weak, the unhealthy, the plus-potentially unhealthy, that the scaphoid type of scapula is most frequently found; conversely, that it is in those found to be innately nearer to such an ideal, the strong, the healthy, the plus-potentially healthy of the race, that the convex type of scapula is most frequently found.

THE AGE INCIDENCE OF SCAPULAR TYPES: TABULATIONS

Attention is next directed to the age incidence of scapular types, a finding as yet unparalleled in mammalian morphology. "That the scaphoid scapula occurs with great frequency among the young, but is relatively infrequent among the old" was a statement made by me in 1911.[11] I have, however, refrained from giving it that degree of emphasis, which after seventeen years of observation and research now seems to be justified. The statement was based on the observations that each scapular type discloses an age incidence, i. e., the convex increases; whereas, the straight, like the concave, decreases in frequency of occurrence with each successive age period from birth to old age when relatively large groups of individuals, representing each successive age period, are investigated. Personal investigations indicate that in the mixed white stocks represented in our population, in the first ten years of life approximately 80 per cent. of such aged persons are possessors of the scaphoid, and approximately only 20 per cent. are possessors of the convex; whereas, in the age period between 70 and 80 years approxi-

mately only 20 per cent. of such aged persons are now the possessors of the scaphoid and approximately 80 per cent. of such are now the possessors of the convex.

A number of independent, rather extensive investigations of similar and dissimilar material in different populations, have been made in reference to percentages of convex, straight and concave scapular types, covering the successive decenniums of life in the living and the dead. The results of some of these investigations have been published and others communicated. The figures secured by all those who had more or less understood the classification, or appreciated the age incidence, or both are arranged in Table 1.

COMMENT

Table 1 contains the classification of 100 fetal scapulae from approximately the tenth week to full-term gestation (‡) and of 1,219 mature skeletal scapulae, whose bearers were of an approximate average of 50 years (§). Twenty-one thousand two hundred and twenty-nine (21,229) observations on living, necropsy, fetal and skeletal material are included in the table; of these, *2,772* represent the dead and 18,457 the living. The material is from various sources, some of which is similar and much of which is dissimilar, and it represents the work of different investigators in classifying human scapulae in the living and the dead. Moreover, the classification of scapulae in the living by independent workers represents phases of physical examination never before attempted. Under such circumstances there are, of course, inaccuracies in the figures which are due either to unavoidable or improper technic, or to lack of complete understanding of the classification. It was not fully understood by Warburg,[16] hence his percentage of "scaphoid" is rather high for the age and nature of his material; nor by Kollert,[24] who did not sharply differentiate between the *straight* and *convex;* hence his figures for *convex* are from 15 to 35 per cent. too high in the several age periods. Cunningham's [15] percentage of *concave,* like that of Weiss, is too high for both the age period and the character of the material. Weiss (†) was forced by public school regulations to examine through the clothing. Cunningham attempted to classify scapular types by exact measurements—something obviously not possible either on living or skeletal material. Nevertheless, the percentage of straight and concave (scaphoid) when combined in the tabulation of both Cunningham and Weiss represent the approximate expectancy in percentages for the respective material and age periods. There are

24. Kollert, V.: Ueber die skaphoide form des Schulterblattes, Wien. klin. Wchnschr. **24**:1299-1301, 1911; Das skaphoide Schulferblatt und seine klinische Bedeutung für Prognose der Lebensdauer, Wien. klin. Wchnschr. **25**:2002-2006, 1912; Interstate Med. J. **21**:1104-1114, 1914 (transation by T. Romeiser).

TABLE 1.—*The Age Incidence of Scapular Types Represented in Prenatal and Postnatal Periods of Life*

Observer and Material	Age Period	Number of Persons	"Convex" per Cent.	"Straight" per Cent.	"Concave" per Cent.	"Straight" + "Concave" = "Scaphoid" Type, %
‡Graves, W. W. Prenatal life, male and female (white), private collection	Approx. 10 wks. to 9 mos. incl.	100	26.0	49.0	25.0	74.0
Graves, W. W. St. Louis Health Show, male and female (white)	3 mos to 67 mos. incl.	422	18.0	56.0	26.0	82.0
§Graves, W. W. Dissecting room, male and female, (mixed stock) various sources	50 approx. aver. age	1,219	54.3	27.0	18.7	45.7
Warburg, F. Cologne Public School (white), male and female	6-7 incl.	1,000	12.6	62.3	25.1	87.9 (?)
†Weiss, W. St. Louis Public School (white), male and female	5-15 incl.	5,325	18.5	29.7 (?)	51.8 (?)	81.5
Graves, W. W. Orphan Asylum (white), approx. 30% of number retarded, male	5-14 incl.	300	11.8	35.2	54.0	89.2
Graves, W. W. Combined St. Louis Infirmary, City Hospital and Masonic Home (white), male and female	40-50	167	54.1	27.4	18.5	45.9
	50-60	174	61.6	24.1	14.3	38.4
	60-70	275	70.0	20.3	9.7	30.0
	70-80	208	81.4	12.7	5.9	18.6
	80-90+	116	88.6	8.3	3.1	12.4
Graves, W. W. Dissecting room, male and female (white), Department of Anatomy Western Reserve University	20-30	45	42.2	33.3	24.5	57.8
	30-40	105	53.3	26.6	20.1	46.7
	40-50	129	60.1	23.2	16.7	39.9
	50-60	88	59.1	26.1	14.8	40.9
	60-70	63	76.2	17.4	6.4	23.8
	70-90	28	82.1	14.3	3.6	17.9
Kollert, V. Necropsies at Institute of Pathological Anatomy, Vienna, Austria, male and female	0-10	308	38.6	34.5	26.9	61.4
	10-20	46	30.4	21.7	47.9	69.6
	20-30	125	53.6	25.6	20.8	46.4
	30-40	116	63.8	21.6	14.6	36.2
	40-50	123	74.8 (?)	22.1	3.1	25.2
	50-60	130	75.4	15.4	9.2	24.6
	60-70	58	72.5	22.4	5.0	27.5
	70-90	34	88.2	8.9	2.9	11.8
Ball and Thomas. Prostitutes (white), California	20-34 +	270	18.0	20.0	62.0	82.0
Cunningham, R. University students, California (white), male and female	16-25	1,057	28.0	15.0 (?)	57.0 (?)	72.0
†Butts, Heber. U.S.N. and M.C. officers and enlisted men (white), 1913	20-30 +	500	67.2	14.4	18.4	32.8
†Ball, J. D. U. S. Army officers in training, 1918	20-30	976	47.6	23.2	29.2	52.4
	30-40	472	54.9	17.6	27.5	45.1
†Ball, J. D. U. S. Army returned overseas men, 1919	20-30	2,738	49.5	37.3	13.2	50.5
	30-40	779	67.3	24.6	8.1	32.7
†Weaver, A. C. U. S. Army hospitalized men, St. Louis	20-83 incl.	939	46.2	18.6	35.2	53.8
†Mackey, D. E. Tabulated from X-ray plates, U. S. Army hospitalized men, Army Medical School	18-30 incl.	1,000	40.6	35.6	23.8	59.4
†Krause, I. B., and Howard, S. P. Missouri State Prison (white), male*	20-40	381	21.0	45.4	33.6	79.0
	40-72	59	30.7	37.7	31.6	69.3
†Staff of Fulton, Missouri, State Hospital for Insane, male and female (white)	20-29	103	19+	47+	33+	80+
	30-39	201	33+	42+	25+	65+
	40-49	326	34+	44+	21+	65+
	50-59	266	39+	45+	15+	60+
	60-69	197	45+	41+	13+	54+
	70 and over	131	49+	35+	15+	50+

* Included in the period 20-40 years are 43 persons under 20 as follows: 1 at 16; 6 at 17; 14 at 18, and 22 at 19 years. In the period 30-72 years: 85 persons are between 30 and 40; 42 between 40 and 50; 9 between 50 and 60, and 8 between 60 and 72. The tabulation represents the first returns from a survey of the entire prison population, numbering approximately 2,500 persons.

† Personal communications.

‡ The collection consists at this time of approximately 400 specimens and the tabulation represents the result of the first hundred examined. The sources of the collection were both local and general but mainly general, in response to an appeal for fetal material published in the J. A. M. A.[11] and other American journals in 1919.

§ The average age of dissecting-room material was approximated: (1) from data on 1,000 bodies, supplied by Dr. Ales Hrdlička and acquired by him in the Anatomical Department, Columbia University (Prof. George S. Huntington) and (2) from data supplied by Dr. D. M. Shoemaker, St. Louis, on 750 bodies distributed to the medical schools of Missouri, in a recent three year period. The range in years of the Missouri material was from 28 to 92; the average age 54.6 years, and that from Columbia University from 15 to 96; average age from 40.8 years. Represented in the tabulation are 198 bones classified in the Departments of Anatomy, St. Louis University School of Medicine and Washington University Medical School; 150 bones in the Department of Anatomy, University of Berlin; 602 bones in the Wistar Institute of Anatomy and Biology, and 269 bones in the United States National Museum (Huntington collection): total, 1,219 bones with approximate average age of bearers of 50 years. The following table, recently compiled by Prof. T. Wingate Todd, Western Reserve University, here published with his permission, gives the first exact information on minimum, maximum and average age of white and negro male and white and negro female dissecting-room material:

	Number of Skeletons	Minimum	Maximum	Average
Male white	564	18	88	48.9
Female white	74	16	80	42.8
Male negro	178	17	70	35.7
Female negro	44	16	87	38.7
Total	860	16	88	43.6

doubtless other inaccuracies in the tabulations, including my own. By establishing uniform methods in recognizing, recording and tabulating scapular types, as suggested in the concluding paragraphs of this communication, avoidable or improper methods leading to inaccuracies should be reduced to a minimum in future work.

The personal equation, however accurate one may be in any endeavor, is a factor that must always be considered. This equation is doubtless represented in the results of every investigation tabulated above. Notwithstanding the personal equation, the inaccuracies in the table and the lack of uniformity in the material, the figures from different sources representing similar material show striking similarities. The age incidence of each scapular type is shown by the percentages found in practically any two successive age periods in the tabulation of Ball, Kollert and myself. Careful consideration of Table 1 makes it apparent that there is a gradual decrease in the percentage of scaphoids (straight and concave), and a gradual increase in percentage of the convex in successive decenniums. This fact supplies an additional biologic reason for combining the *straight* and *concave* into a single type, namely, the *scaphoid*. Moreover, the figures justify authors of textbooks in describing and picturing the scapular vertebral border as more or less convex, because the figures show that the convex is still the predominating type in living and anatomic material in our population after the fifth decennium of life, which decennium represents the average age of anatomic material.

Having pointed out the nature of, and the lack of uniformity in, the material and the reasons for the inaccuracies in the investigations, attention is now directed to some of the studies bearing on the possible significance of the age incidence of scapular types: (1) To the unusually large percentage of the scaphoid type in German public school children, aged from 6 to 7 years (Warburg [16]), and also to the approximately correct percentage of this type in St. Louis public school children, aged from 5 to 14 years (Weiss †); (2) to the relatively large percentage of the scaphoids in university students, aged from 16 to 25 (Cunningham [15]), and to the contrast of the figures in that study with those on prostitutes, aged from 20 to 34 years, in the same territory, giving a larger percentage of scaphoids even at a greater age period (Ball and Thomas [25]); (3) to the splendid investigations of Ball (†) on officers in training and returned overseas men, and (4) to those of Butts (†) on U. S. Navy and Marine Corps officers and men, of Weaver (†) on hospitalized overseas men and of Mackey (†) on roentgen-ray plates on U. S. ex-service men. The groups found in the work of Ball, Butts, Weaver and Mackey have

25. Ball, J. D., and Thomas, H. G.: A Sociological, Neurological, Serological and Psychiatrical Study of a Group of Prostitutes, Am. J. Insan. **74**:647-666, 1917-1918.

this in common that they represent the most rigid selection by physical and mental tests of the army and navy. Weaver's and Mackey's groups of ex-service hospitalized men show somewhat larger percentages of scaphoids than do the groups of Ball and Butts for approximately the same age periods. In this connection, the army, navy and university groups lend themselves to comparison with the prostitute group and with the prison group (Krause and Howard, and with Fulton, Missouri State Hospital group †). Special attention is called to the remarkable group of Kollert, representing 1,000 necropsies from before birth to old age. Finally, attention is called to (*a*) the more rapid decrease of the *concave* than the *straight* in successive age periods: (*b*) to the more rapid *decrease* in the straight and concave; conversely, to the more rapid *increase* in the convex after than before the maturity of the human scapula (from the 20th to 25th year of life). No further comment, at this place, seems necessary other than that the figures are meager, indeed, when compared with their possible significance. They show beyond all cavil or doubt just what they are intended to show; that each scapular type has an age incidence. The figures establish that fact, but they do not and cannot explain it. Its explanation is an important problem in connection with human morphogenesis.

THE PROBLEM: TWO POSSIBLE EXPLANATIONS

The relative frequency of convex and scaphoid types in all periods of life, and striking difference in their percentages in the extremes of life postulate two possible explanations of the age incidence. First the scaphoid is changed into the convex in most individuals during the course of years. Second, the scaphoid is not changed into the convex during the course of years. If ample evidence can be found in support of the first explanation, we shall then establish a finding heretofore unrecognized in mammalian ontogenesis; on the other hand, if we can find ample evidence in support of the second explanation, we shall then establish some relation of the age incidence of the types of one morphologic feature (the scapula) to longevity, and if to longevity, to morbidity and adaptability in general. From the very outset of my investigations, it was obvious that change of one type into another implied natural processes of bone growth, or modification of natural processes by muscle influence (variation, pull), or by disease, or by environmental influence. Moreover, it was obvious that natural processes, whether modified or not, become operative very early in prenatal life and persist throughout development into maturity and senescence. The problem from the beginning has been and is: What is the tenable explanation of the age incidence? This problem has been approached from various angles, but space forbids more than mentioning the scope of investigations and some of the results with brief comment on them.

SCOPE OF INVESTIGATIONS

(1) Comparative anatomy of scapulae and of other bones, and consideration of the literature on this subject and on normal bone growth and its possible modification by environmental influences from birth to old age; (2) morphology of human scapulae in prenatal and postnatal growth periods to maturity (25th year of life) and onward;[11] (3) morphology of scapulae in several lower mammalian families during prenatal and postnatal life periods; (4) variations of muscles and their attachments in relation to scapular types in fetal and postnatal periods of human life; (5) age changes of human and other mammalian scapulae from birth to maturity and from maturity to old age;[11] (6) racial occurrence and distribution of scapular types in ancient and modern man;[11] (7) relation of scapular types to sex, race, stock, type, build and of modifying influences on scapular types of environment, including occupation, social level, health, disease (rickets, endocrine disturbances, paralysis) amputations, etc.; (8) heretofore, recognized anatomic, physiologic, mental and moral inherited variations coexistent with each scapular type;[11] (9) possible modifying influence on the degrees of convexity and concavity of scapular types by right or left handedness; (10) scapular type (vertebral border) symmetry and asymmetry from the tenth fetal week onward throughout postnatal life periods; (11) comparative studies of detached individuals, of individuals of families and of so-called "normal" and "abnormal" groups; (12) follow-up observations on a number of individuals, representing successive age periods in reference to the possibility of change of one type into another both during growth periods and after maturity.[11]

RESULTS

Some of the results of the foregoing investigations have already been briefly summarized in this paper; some are published, some are still unpublished, and none is complete.

1. At approximately ten weeks in development the human scapula has attained the general form and particular type which it apparently ever afterward retains and, with but few exceptions, it becomes completely ossified (mature bone) between the 20th and 25th year of life. Even prior to the tenth fetal week, reconstructed serial sections of the shoulder girdle (Hagen,[26] Bardeen and Lewis[27] and Lewis[28]) have revealed the presence of convex and concave types.

26. Hagen, W.: Die Bildung des Knorpelskelets beim meuschlichen Embryo, Arch. f. Anat. u. Entwicklungs geschichte, 1900, p. 1.

27. Bardeen, C. R., and Lewis, W. H.: Development of the Limbs, Body Wall and Back in Man, Am. J. Anat. **1**:1, 1901-1902.

28. Lewis, W. H.: Development of the Arm in Man, Ibid., p. 145.

2. Change of the scaphoid into the convex at any time after type formation and during subsequent life periods implies not merely an alteration in vertebral border contour but a reconstruction or remodeling of the entire bone, an event wholly unparalleled in bone growth and one wholly without precedent in the human skeleton incident to any natural process as yet known.

3. The analogies of skull forms, and the form or character of other discernible inherited morphologic features, show that the types of such features remain more or less fixed throughout the subsequent life of the individual from early life to maturity and onward. It is, therefore, wholly improbable that the human scapula could be the only discernible morphologic feature whose types are completely changed from one into another both during and after the developmental periods of life.

4. Particular variations of scapular muscles or of their attachments have not been found to be associated exclusively with any particular scapular type in any period of life, either in my dissections or in those of others. Such variations cannot be interpreted as causes of scapular types as recently inferred by Balli;[20] rather are they to be interpreted as associated variations. Inherited variations of bones, muscles and of morphologic features generally have heretofore been considered expressions of the anlage peculiar to the individual in which they are found. The influence of muscles, or of their attachments, or of muscle variations, or of muscle pull, either on scapular type formation, alteration or modification must be considered negligible when we remember that as early as the tenth fetal week each scapular type is found.

5. Convex, straight and concave types are found in all postnatal life periods in varying degrees and percentages in the tall, the short, the fat, the lean, the broad backs, the narrow backs, the weak, the strong, the healthy, the sick, the near to and the remote from, the ideal in development, the mentally brilliant, average and defective, the well and poorly muscled, the "excellent," "good" and "poor" types, regardless of race, stock, sex, social level, occupation or environment.

6. Scapular type symmetries and asymmetries (comparing one vertebral border with the other) are found in both prenatal and postnatal life periods from the tenth fetal week onward. Occasionally one finds an individual with convex on one side and concave on the other, and a rather frequent finding is straight on one side and concave on the other. Similar scapular type symmetries and asymmetries are found in immature and mature mammalian scapulae (orang-utan, gorilla, chimpanzee, flying lemur, bat, armadillo, hedgehog, etc.). The presence of all such scapular type asymmetries both in prenatal and postnatal life periods show them to be independent of right or left handedness, independent of occupation and other environmental influences.

Usually similar, but occasionally dissimilar, types are found in twins both in prenatal and postnatal life periods. Draeseke [14] reports male twins one of which has convex scapulae; the other concave scapulae.

7. The finding of similar scapular types in ancient and modern man; their racial distribution; their hereditary nature and the finding of similar types in some lower mammals leave but little foundation for the assumption that the human scapula, by any natural process as yet known, becomes changed in type at any time after its earliest type formation.

8. The increase in the percentages of the convex and the decrease in the percentages of the scaphoid (occurring more rapidly after than before maturity), lead to the reasonable conclusion that neither natural processes of bone growth or their modifications change the scaphoid into the convex either before or after maturity of the bone. Not only do the figures in Table 1 justify this conclusion, but every investigation thus far undertaken justifies it.

9. Realizing that final and complete explanation of the age incidence depended on follow-up observations on a number of individuals from birth to maturity and onward, I began such observations on approximately 200 individuals, representing successive age periods, in 1907. Thus far scapular types have remained fixed not only during life periods after maturity but also during periods of growth and development.

Considering the scope and results of investigations herein outlined, it appears that one type of scapula is not changed into another at any time during a person's development and life.

THE USEFULNESS OF SCAPULAR TYPES

The usefulness of scapular types is firmly grounded in their relations to problems of heredity and longevity. Obviously, if they do not change, our figures indicate decreased mortality in many of those possessing the convex and increased mortality in many of those possessing the scaphoid. Our figures, however, express the results of observations on the inherited types of only one part of man's makeup; hence they are for this and other obvious reasons neither similar, nor are they comparable, to those of life and mortality tables. Nevertheless, they bring unmistakable evidence in support of a variable relation of heredity to longevity, a relation long recognized by physicians, biologists and biometricians. A recent mathematical discussion by Pearl [29] "Indicates that from one-half to three-fourths of the death rate is selective in character, because that proportion is determined by hereditary factors. Just in proportion as heredity determines the death rate, so is the mortality selective."

29. Pearl, Raymond: The Biology of Death, p. 177, J. B. Lippincott Co., 1922.

I here merely suggest that scapular types may serve as useful aids in recognizing those hereditary factors on which a portion of "selective" mortality and morbidity depend.

The relations of scapular types to problems of heredity and longevity, and the contrast between scapular type percentages of dissimilar material for similar age periods (Table 1) justifies the inference of inherent strength (good adaptations) and decreased morbidity in many of those possessing the convex; conversely, the inference of inherent

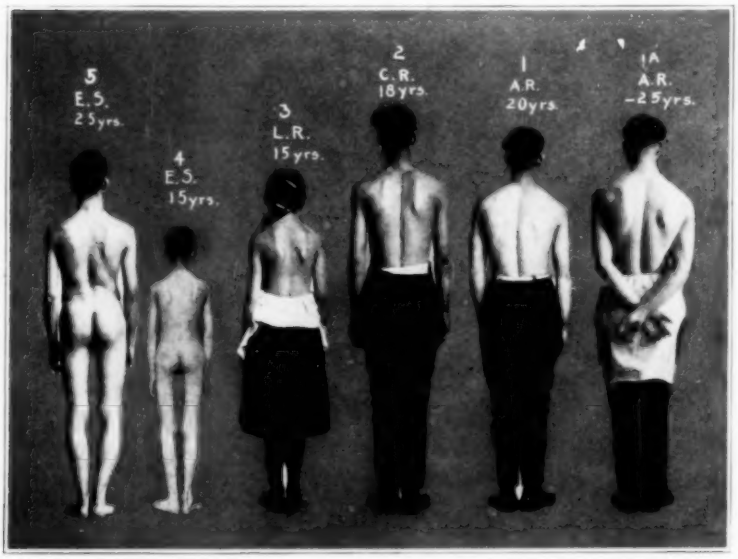

Fig. 4.—Scapular types, after several years growth in the progeny of the R1 family and in E. S., a member of the S12 family. Compare Figures 1, 2, 3 and 1A with those of the same persons shown in Figure 1. Figures 4 and 5 represent E. S. at 15 and 25 years of age.

weakness (poor adaptations) and increased morbidity in many of those possessing the scaphoid.

We have long known that all human beings are susceptible to disease; some more, some less. The questions are therefore pertinent, who among us in the broadest sense, are the more susceptible? Who are the more immune? We do not yet study the apparently healthy persons as intensively as we study the definitely sick. We do not yet investigate all the discernible inborn factors underlying health or disease. Just so long as we fail to search for the innate differences in persons, we shall fail to

appreciate the soil factors, or capacities, underlying health or disease and shall fall short of the possibilities in disease recognition, prevention and cure.

The investigations of Kollert,[24] Reye,[13] Nonne,[30] Thielke,[19] Draeseke,[14] Chotzen,[31] Kellner,[32] Clemens,[33] Ball and Thomas,[25] Mackey † and Hosteing,[18] as well as my own,[11] have shown that the scaphoid type of scapula is more frequently coexistent than is the convex, with a basic pathology, with an inborn unduly disease susceptible soil.

SUMMARY AND CONCLUSIONS

1. Observations on the R 1 family, in 1906, led me to classify human scapulae into convex, straight and concave types and to designate both the straight and concave the scaphoid.

2. Investigations of living, fetal and skeletal (ancient and modern) material and of lower mammalian material revealed the hereditary nature, primal origin, of each scapular type.

3. Comparative clinical and anthropometric studies of members of families through as many generations as possible showed that scapular type inheritance is usually dependent on scapular type matings, and that disease and possibly other poison factors may occasionally "alter" such inheritance.

4. Investigations of comparable groups, representing living, necropsy and skeletal material of known age disclosed a finding as yet unparalleled in mammalian morphology: the age incidence of scapular types, i. e., the convex increases while the straight and concave decrease in frequency of occurrence in successive age periods from birth to old age.

5. The age incidence required explanation; hence investigations were inaugurated to determine whether one scapular type changes into another. The results of the investigations justify the conclusions: (1) that no natural process or circumstance as yet known changes the scaphoid into the convex after earliest type formation (approximately tenth fetal week); and (2) that the scaphoid is more often found than is the convex in the plus-potentially sick, the shorter-lived of the race.

6. While our investigations are in no particular complete, nevertheless the results thus far secured clearly show the usefulness of scapular types in studies of human heredity, longevity, morbidity and adaptability in general. Scapular types, however, are not standards with which we

30. Nonne, M.: Scapula scaphoidea (Graves), Deutsch. med. Wchnschr. **43**: 159, 1917.

31. Chotzen, F.: Ueber vorkommen Bedeutung der Scapula scaphoidaea, Berl. klin. Wchnschr. **55**:949, 1918.

32. Kellner: Scapulae Scaphoidaea, Deutsch. med. Wchnschr. **37**:94, 1911.

33. Clemens, D.: Syphilis u. Schwachsinns, Ztschr. f. d. Exforsch. u. Behandl. d. Tugendliche Schwachsinns **6**:353-357, 1912.

may measure man, any of his structures or any of his functions. A particular scapular type is only one part of an individual's inheritance; hence it is a conditional, not an absolute index of constitution.

7. The finding of the age incidence of scapular types disclosed the heretofore unrecognized principle of investigating inherited variations, whether of structure or function, in successive age periods from early life to old age. Further application of this principle gives promise of finding other age incidences of similar import.

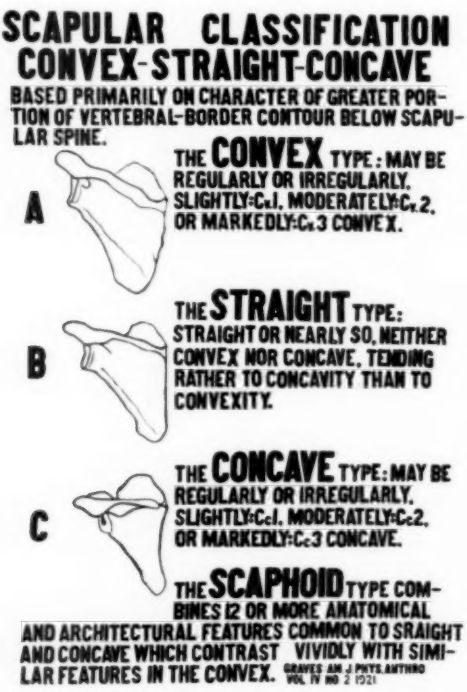
SCAPULAR CLASSIFICATION
CONVEX-STRAIGHT-CONCAVE
BASED PRIMARILY ON CHARACTER OF GREATER PORTION OF VERTEBRAL-BORDER CONTOUR BELOW SCAPULAR SPINE.
A
THE CONVEX TYPE: MAY BE REGULARLY OR IRREGULARLY, SLIGHTLY: Cv1, MODERATELY: Cv2, OR MARKEDLY: Cv3 CONVEX.
B
THE STRAIGHT TYPE: STRAIGHT OR NEARLY SO, NEITHER CONVEX NOR CONCAVE, TENDING RATHER TO CONCAVITY THAN TO CONVEXITY.
C
THE CONCAVE TYPE: MAY BE REGULARLY OR IRREGULARLY, SLIGHTLY: Cc1, MODERATELY: Cc2, OR MARKEDLY: Cc3 CONCAVE.
THE SCAPHOID TYPE COMBINES 12 OR MORE ANATOMICAL AND ARCHITECTURAL FEATURES COMMON TO SRAIGHT AND CONCAVE WHICH CONTRAST VIVIDLY WITH SIMILAR FEATURES IN THE CONVEX.
GRAVES AM J PHYS ANTHRO VOL IV NO 2 1921

Fig. 5.—Outline drawings, by P. A. Conrath. A-Convex "Cv2" type; B-Straight "St." (saphoid) type, and C-Concave "Cc3" (scaphoid) type.

POSSIBILITIES OF FURTHER RESEARCH

Since human beings differ in their innate capacities for adaptation, inherited variations represent vital and practical problems of biology and clinical medicine, meriting general research in the following directions: (*a*) Further use of ascendants and collaterals as biologic standards in comparative anthropometric and clinical studies of families, through as many generations as possible, in reference to "normal" and "altered"

inheritance of scapular types and of other variations; (*b*) Accumulation of additional data on the age incidence of scapular types in so-called "normal" and "abnormal" groups of living, necropsy and skeletal material of known age in successive age periods; (*c*) More information bearing on the explanation of the age incidence as may be secured from further follow-up observations; and (*d*) Further investigation of the relations of scapular types and other inherited variations to problems of heredity, longevity, morbidity and adaptability in general. These lines of endeavor may lead to a fuller appreciation of individual constitution and to a clearer recognition of the factors of heredity and environment underlying health and disease, racial betterment and racial deterioration.

METHODS OF RECOGNIZING, RECORDING AND TABULATING SCAPULAR TYPES

Remembering the classification described and pictured in Figure 5, one will seldom find a scapula in the living subject that cannot be readily classified by inspection and palpation, except in obese individuals, and in such the roentgen ray may be employed.[11] In order that the personal equation and avoidable inaccuracies in scapular classification on the living may be minimized the following methods and precautions are suggested:

Inspection.—While the subject is stripped, at least to the waist line, and standing at ease in a good light, one should note general development and attitudes, topography of trunk, form of chest, course of clavicles, right and left acromial level, squared, drooped or rounded shoulders, spinal curves, length of neck and the relation of scapular vertebral borders to vertebral axis. The modeling of these borders below the scapular spine may be seen in most persons. Regardless of type the vertebral border may be prominent, wing-like (scapula alata). The dimensions and form of the interscapular space below the scapular spine are dependable signs of type. It is often narrowed in the convex; widened in the straight and concave. Usually in the convex, the form of this space is roughly A-shaped, the general direction of the vertebral border is downward and outward, the inferior angle of each bone is from 1 to 4 cm. further away from the vertebral axis than is the base of the scapular spine. As a rule, in the straight or concave the base of of the scapular spine and the inferior angle are equidistant, or nearly so, from the vertebral axis, the form of the interscapular space is roughly H-shaped, but in some instances it is roughly V-shaped: the general direction of each vertebral border is downward and inward.

Palpation.—Asymmetries in type (mixed types) and differences in degree of convexity or concavity render it necessary to palpate the

contour of each vertebral border. In mixed types one occasionally finds convex + concave, more frequently convex + straight and still more frequently straight + concave. One may bring out the contour of each vertebral border by several methods, but the following have been found to be reliable: (1) If the examiner is right-handed, he should face and stand close to the left side of the subject, place his left hand over upper portion of the subject's right arm and bring rather firm pressure to bear between his own left arm and chest on the subject's shoulder-girdle regions. (2) The examiner flexes the subject's pronated forearms and places them over the small of the back. One may combine both methods and thus secure a control.

The prime purpose of either or any method is to bring about greater relaxation of rhomboid and trapezius muscles, and to elevate the vertebral borders from the chest wall. With this accomplished, one may now more readily see their modeling, palpate and compare them. Palpation should be made at a right angle or nearly so with the contour of the vertebral border, slowly and firmly without pain or discomfort to the subject. Undue haste or force defeats the purpose by exciting muscle contraction and resistance. The classification, as well as the degree of convexity or concavity, should now be determined. During palpation the examiner should neither see nor feel contractions of shoulder-girdle muscles, and especially in the rhomboid and trapezius. If contractions in these muscles are seen or felt, the findings may be faulty; for example, a straight or moderately concave may be called a convex.

Roentgen-Ray Examination.—Except in the obese, this method is less reliable than combined inspection and palpation because of possible shadow distortion. In age periods prior to 16 years in living subjects, it is likely to be unreliable, because the vertebral border and the inferior angle regions are still partly cartilage, and the cartilage is but dimly, if at all, shown by the roentgen ray. In such examination the subject should rest with the back on a plate, with the arms resting close to the sides and forearms in a position of moderate supination. In this position one will secure the least distortion of vertebral border shadows.

Recording.—Because "mixed types" occur, the record should show classification of each scapula. If the greater part of the vertebral border between base of scapular spine and inferior angle region is found to be convex, depending on the degree of convexity, it is recorded Cv1, Cv2 or Cv3. If the greater part of this portion of the border is found to be straight, it is recorded St., and if concave, depending on the degree of concavity, it is recorded Cc1, Cc2 or Cc3. One should always keep a record of those individuals whose scapulae cannot be classified and give reason: obese, resistant or anatomic.

Tabulation.—In tabulating the results of classification in each age period, one should arrange columns headed age period, convex, straight, concave and other columns headed convex + straight, convex + concave, straight + concave, not classified. A tabular form for the age period from 10 to 19 years, representing scapular classification of 500 persons let us assume to be as follows:

TABLE 2.—*Age Period, Representing Scapular Classification of Five Hundred Persons*

Age Period	Convex		Straight		Concave		Convex + Straight		Convex + Concave		Straight + Concave		Not Classified		Total	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
10 to	110	22	190	38	100	20	25	5	5	1	60	12	10	2	500	100
	12.5		12.5		2.5		25		5		60					
19 yrs.	2.5		30		20		—	—	—	—	—	—				
							2		2		2					
							(12.5 Cv.)		(2.5 Cv.)		(30 St.)					
							(12.5 St.)		(2.5 Ce.)		(30 Ce.)					
	125		232.5		132.5								10		500	
	25%		46.5%		26.5%									2%		100%

Mixed types: 25 + 5 + 60 = 90
5% + 1% + 12% = 18%

The percentages in the columns headed convex, straight or concave in the group of 500 are readily calculated. The results, however, would not represent the percentages of all types in the entire group, because the "mixed" types have not yet been divided and apportioned. The total number of persons in each mixed type column should now be divided equally and one-half of the number apportioned to each column represented in a given "mixed type." For example, we find twenty-five individuals in the column headed "convex + straight"; 12.5 of this number is now added to the column headed "convex" and 12.5 to the column headed "straight." We find in the column headed "convex + concave" five individuals, and similarly dividing this number we add 2.5 to the column headed "convex" and 2.5 to the column headed "concave." Similarly dividing and apportioning the number found in the "straight + concave" column gives the total scapular classification expressed in numbers and percentages as above. One should also figure and tabulate (as above) the percentages of the "mixed-type" and of the "not-classified" columns in each age period for comparison with other age periods, other material and with the tabulations of other examiners.

Data for Correlation.—In the study of persons singly or in groups, the following data are indispensable: age, sex, race or stock, occupation, social condition, mental level, weight, standing height and in the sick the clinical diagnosis. Much to be desired additional data for correlation are sitting height, anteroposterior and transverse skull and chest measurements, associated asymmetries, disproportions, disharmonies of

structures and functions, including those discernible variations usually called stigmas. For a summary of so-called stigmas see the article of Walton.[34] For all anthropometric measurements the methods given by Hrdlička [35] are recommended.

34. Walton, G. L.: See Posey and Spiller, The Eye and the Nervous System, Philadelphia, J. B. Lippincott Company, 1906, pp. 950-971.

35. Hrdlička, A.: Anthropometry, Philadelphia, Wistar Institute of Biology and Anatomy, 1920.

PRIMARY SARCOMA OF THE STOMACH *

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That primary sarcoma of the stomach is rare has been recognized by our pathologists. Several writers have collected reports of these tumors. In 1900, Fenwick [1] collected sixty cases in the literature and concluded that fifty-three were authentic. Flebbe,[2] in 1914, collected 157 cases. Haggard [3] collected 244 cases in 1920.

The rarity of these tumors is readily seen from this list: One sarcoma of stomach in 840 specimens (Berlin Pathological Institute), six in 13,387 necropsies (Hirsch), and eight in 2,069 malignancies of stomach (Mayo clinic during five years).

Ewing [4] has stated that sarcoma of the stomach constitutes 1 per cent. of gastric tumors.

The following case came under my observation while in charge of the first medical division pathological department of Columbia University at Bellevue Hospital.

REPORT OF CASE

G. D., a man, aged 77, Roumanian, single, was admitted to hospital Jan. 12, 1923, with a history of weakness for the last three months. He had had gonorrhea and syphilis (fifty years ago), pneumonia and furunculosis (two years ago). There was no history of any injury. His father and mother had died of "old age." One brother was living and well and another had died of heart trouble. There was no history of any chronic disease in the family, or tobacco or alcohol.

Three months previous to admittance the patient became unconscious in the street. The onset was sudden, with weakness. There was no paralysis or injury. He was taken home and became conscious, with the intense weakness continuing. His appetite had been poor for three months, although there was no distaste for food. There was no vomiting, headaches or abdominal pain. There was burning in the epigastrium of four months' duration, with difficulty in swallowing. The patient had been losing considerable weight for several years. He occasionally had a productive cough. The bowels were constipated. There was no pain. He rose once during the night to urinate, otherwise his sleep was fair. His vision was poor and the left eye was blind. He had weighed 220 pounds (99 kg.) and now weighed 175 pounds (74.9 kg.). The loss had been rapid.

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* From the Department of Physiology, Columbia University.

1. Fenwick: Primary Sarcoma of the Stomach, Lancet **1**:463 (Jan.) 1901.
2. Flebbe: Ueber das Magensarkom, Ztschr. f. exper. Path. u. Therap. **12**:311-336, 1913.
3. Haggard, W. D.: Sarcoma of the Stomach, Surg., Gynec. & Obst. **31**:505 (Nov.) 1920.
4. Ewing, James: Neoplastic Diseases, Philadelphia, W. B. Saunders Company, 1919.

At the time of examination the patient was lying quietly in bed and looked chronically ill. The conjunctivae were slightly injected, and there was a cataract of the left eye and arcus senilis. Several teeth were missing, several had been filled and the remainder were carious with slight pyorrhea beginning. The tongue was dry and coated, protruding in the midline. There were no abnormal masses or pulsations in the neck. The chest was symmetrical but hyperresonant throughout. The pulse was small and regular with sclerotic vessels. The heart was enlarged to the left and the sounds were poor in quality. The abdomen was slightly retracted and a mass was felt in the epigastrium. The liver was palpable, three finger breadths below the costal margin. The skin was dry and atrophic and there was moderate adenopathy. There were slight petechial edema of both legs. The blood pressure, taken on the right arm, was: systolic 105, diastolic 65. The urine was acid with no albumin and a specific gravity of 1.020. The stool was black and gave a positive guaiac reaction. The red cell count was 2,800,000, the white cell count was 16,000 and the hemoglobin was 45 per cent. The nonprotein nitrogen in the blood was 48 mg., the creatinin

Fig. 1.—The stomach, showing the sarcoma in the cardiac region.

1.8 mg., and the uric acid 2.26 mg. The patient died Jan. 16, 1923. The diagnosis was as follows: neoplasm of the stomach; arteriosclerosis (general); chronic myocarditis; senility.

Necropsy.—The body was that of a well developed white man, about 78 years of age, 5 feet 9 inches (164 cm.) in height. The skin was much wrinkled. The hair distribution was normal. There were no noticeable changes in the external nares, mouth, ears or eyes. The external genitalia were normal.

Abdomen.—A midline incision was made in the trunk in front. The peritoneum was smooth and glistening. The diaphragm extended upward to the fifth interspace on the right, and to the upper margin of the sixth rib on the left.

Chest.—There was considerable yellow fat over the pericardium. The pleural cavities were dry. The lungs were normally free.

Heart.—The visceral and parietal layers of the pericardium were smooth and glistening, and contained the normal amount of straw colored fluid. The heart was normal in size. In the right side of the heart there was a small quantity of deep red, partially clotted and fluid blood. The auriculoventricular junction admitted the entrance of two fingers. The endocardium of the right side of the heart was well preserved and the pulmonary valves and pulmonary artery were normal. The endocardium of the left side of the heart was normal. The mitral

valve was unchanged. The aortic valves were slightly thickened. The surfaces made by sectioning the heart muscle were dark red.

Lungs.—These were easily removed. They were large, of normal weight and they crepitated throughout. On the surface of both lungs there were mottled white and black regions. These black regions were more marked at the apices. The surfaces made by sectioning had a few white nodules, the size of a pinhead, firm, and extended slightly over these surfaces. The mucosa of the large bronchi was normal. The peribronchial lymph glands were not enlarged.

Fig. 2.—The liver with the metastatic nodules of the sarcoma.

Spleen.—There was no noteworthy gross pathologic change.

Pancreas.—It was small and pink. The surfaces made by sectioning were normal.

Suprarenals.—They were small. The cortices were narrow and yellow. The medullae were smooth and gray.

Kidneys.—They were small and embedded in fat. Their capsules were thickened, and stripped with difficulty, leaving a granular surface. They did not cut easily. The cortices and medullae were not well differentiated and the cortices were contracted. The pelves contained a small amount of fat.

Urinary Bladder.—It was slightly distended with amber colored urine. The mucosa was pale. The openings of the ureters were patent.

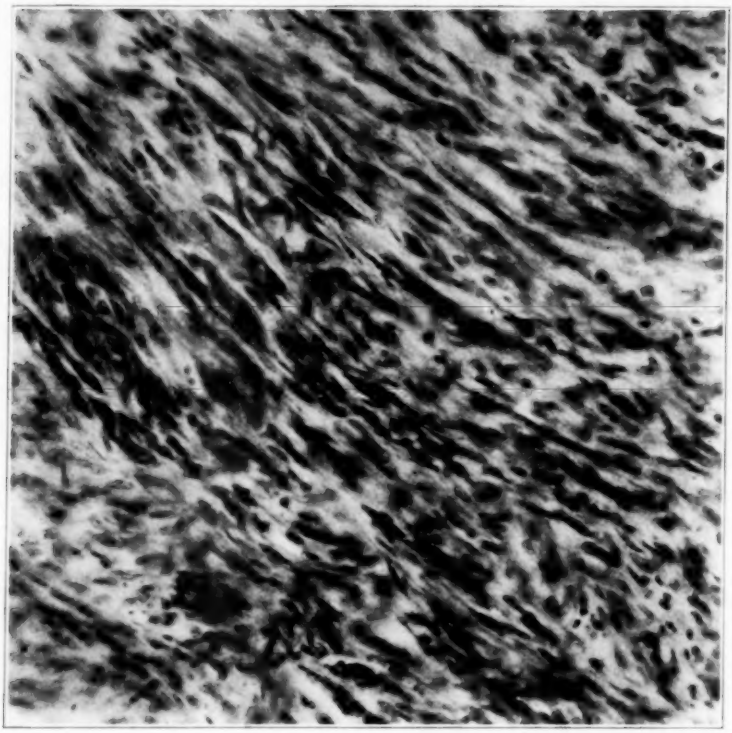

Fig. 3.—Microscopic section of the large spindle cell sarcoma of the stomach.

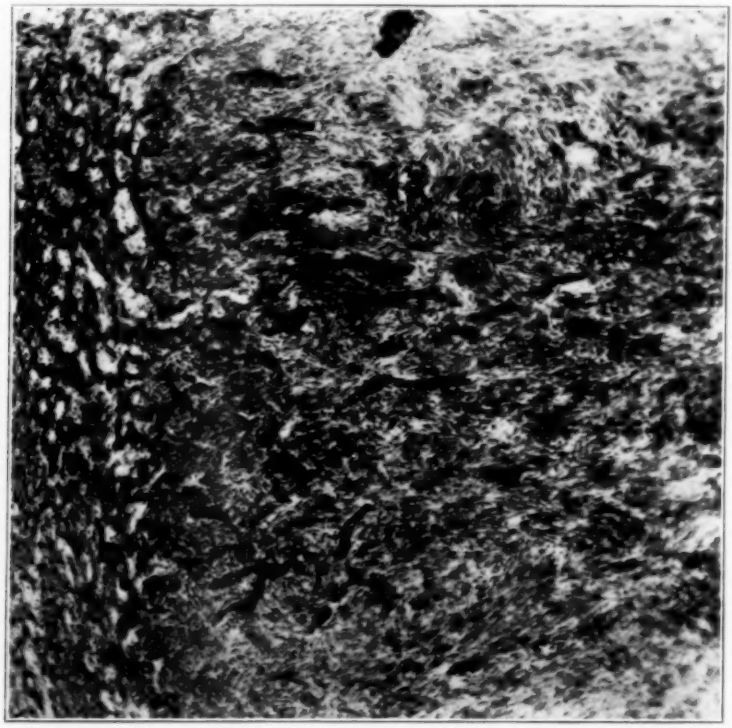

Fig. 4.—Microscopic section of the spindle cell sarcoma of the liver. Note islands of pyknotic liver cells intermingled with the tumor cells.

Prostate Gland.—There was no marked gross pathologic change.

Testicles.—They were small. The surfaces made by sectioning were smooth and yellow. The tubules were easily removed.

Aorta.—The abdominal and thoracic aortae were normal in caliber and thickness. There were a few small yellow plaques about from 2 to 4 mm. in diameter in the abdominal aorta.

Lymph Nodes.—The retroperitoneal lymph nodes were unchanged. The organs of the neck and brain were not examined.

Stomach.—The tumor was located at the cardiac portion, and was 13 cm. wide and 10.3 cm. long. It was 5 cm. thick near the center, firm, hard, grayish white and cut with resistance. Most of the tumor mass was along the greater curvature. The center of the tumor was markedly ulcerated, soft and irregular. The surfaces made by sectioning had a fibrous appearance. The outer surface of the stomach in the region of the tumor was the size of an ostrich egg and was markedly adherent to the diaphragmatic surface. The stomach weighed 1,680 gm. It was larger than normal. From the lower edge of the tumor to the pylorus it was 18.2 cm. long and averaged 8.5 cm. wide. The rugae were distinct and the surfaces were mammillated.

Liver.—It weighed 1,055 gm., and was studded with huge nodules, the largest measuring 2 by 1.8 cm. in its largest diameter, and the smallest 1 by 2 mm. These nodules were umbilicated, grayish yellow, hard and cut with resistance. On the surfaces made by sectioning there were a few small, transparent regions surrounded by darker yellow zones. The centers were often necrotic. These surfaces were grayish yellow and had a fibrous-like arrangement of the tissue. The lower surface of the inferior lobe was not so greatly involved as the upper portion, but the surfaces made by sectioning had as much involvement.

Anatomic Diagnosis.—Primary neoplasm of the cardiac portion of the stomach; metastatic neoplasm of the liver; chronic interstitial nephritis; emphysema of the lungs; general arteriosclerosis.

Microscopic Pathology.—The cells in the tumor were arranged in bundles and had replaced the normal tissue. The bundles and cells were closely packed together. The cells were spindle shaped and the majority were large, hyperchromatic and irregular. The nuclei contained much chromatin and there were nucleoli in 80 per cent. of the cells.

Liver.—The nodules contained cells closely resembling those described in the foregoing paragraph. Normal liver tissue surrounded these nodules, but the liver cells immediately surrounding the tumors were pyknotic and loosely arranged. On the outer edge of the nodules were islands of pyknotic liver cells.

Microscopic Diagnosis.—Large spindle-cell sarcoma of the stomach, with metastatic sarcoma of the liver.

CALCIFICATION OF THE HEART: ITS ROENTGENOLOGIC DEMONSTRATION

REVIEW OF LITERATURE AND THEORIES ON MYOCARDIAL CALCIFICATION *

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The case presented herewith is the first one on record in which calcification of the heart muscle itself, without involvement of the pericardium, has been demonstrated radiographically intra vitam, and in which the roentgen-ray diagnosis was confirmed by necropsy. The finding was detected accidentally, in the course of a special type of roentgenologic investigations carried on for several years at the Montefiore Home and Hospital. After two years of comparative radiographic and gross pathologic studies on a large scale it was found that quite often pathologic conditions which could have been diagnosed roentgenologically very easily, had been overlooked intra vitam owing to the fact that they had not given rise to any clinical symptoms. It was therefore decided to give every newly admitted patient a brief roentgen-ray examination, to keep records of the roentgen-ray findings, and finally to compare the latter with the clinical and later on with the necropsy findings. With the permission of Dr. S. Wachsmann, at that time Medical Director of the Montefiore Home and Hospital, and with his helpful suggestions (for which most sincere thanks are expressed here), these investigations were continued for several years, in the course of which this case of myocardial calcification was discovered.

The roentgenologic side of the case has been demonstrated previously. Since then the literature on myocardial calcification has been collected, the cases so far published and the theories of the various authors have been studied and classified. The result of the work is herewith given.

In presenting the material, it was deemed advisable first to enumerate the cases published previously and then to describe as the last one of the series my own case, followed by a brief résumé of the various theories on myocardial calcification. In doing so, it is not intended to pose here as a pathologist or as a clinician, but strictly as a clinical roentgenologist, who has to have a sufficient understanding of the clinical as well as gross pathologic side of all those conditions which may come up for consideration roentgenologically, a knowledge of which ought to be con-

* Read before the German Medical Association of New York, Feb. 4, 1924.
* Demonstrated before the New York Physicians Association, March 6, 1919.

sidered absolutely indispensable not only for the clinical roentgenologist but for any qualified roentgen-ray specialist.

For a readier understanding of the following cases it might be well to point out here several fundamental points pertaining to calcification in general, namely: (1) dead tissue, or at least deteriorated tissue, appears to be a place of predilection for calcium deposits; (2) as calcium is excreted mainly through the kidneys, intestine and bronchi, interference with its excretion in those organs may become a causative factor for abnormal calcium deposits within the body tissues; (3) freeing of large amounts of calcium within the body, for instance, by extensive bone destructive processes, may cause an overloading of the circulation by calcium salts, followed by secondary calcium deposits in apparently healthy tissues: the so-called calcium metastasis of Virchow;[1] (4) as in the lung, the stomach, and the kidneys acids are excreted into cavities, there may be left an increased alkalinity of the fluids in the substance of the organs mentioned. This increased alkalinity makes the calcium salts decidedly less soluble and may thus aid under certain conditions in the causation of calcium deposits in those organs.

REVIEW OF THE LITERATURE

Morgagni,[2] in his excellent work published in 1762, briefly mentions a case of calcification of the heart. He also has collected a few similar cases without giving any further details.

In 1768, M. Bordenave[3] cites the case of a man, aged 50 years, who had been suffering for a long time from cardiac insufficiency. Necropsy showed a bilateral hydrothorax, adhesive pericarditis, and myocardial calcification "of unequal thickness and in some places 2 inches (5 cm.) in breadth." This calcification involved the "whole of the right ventricle from the basis to the apex of the heart and following the course of the septum, ascended from the apex about half way up the left ventricle."

An interesting case of extensive myocardial calcification was published in 1783 by Samuel Foart Simmons and Henry Watson,[4] the former giving a review of the clinical side, the latter describing the necropsy findings. The article was published in 1783. This volume is interesting not only because it contains the first well described case of myocardial calcification, together with an illustration (Fig. 1) of the

1. Virchow: Ueber Kalkmetastase, Virchows Arch. f. path. Anat. **8**:103, 1855; **9**:618, 1855.

2. Morgagni: De Sedibus and Causis Morborum, 1762, epist. 27, art. 16, etc.

3. Bordenave, M.: A Case of Ossification of the Heart, Mém. Acad. de sc., Paris, 1768.

4. Simmons, S. F., and Watson, H.: A Case of Ossification of the Heart, London Medical Communications, 1783, p. 228.

necropsy specimen, but also because it gives a detailed account of the great influenza epidemic of the year 1782. One is reminded, when reading that report, of the last influenza epidemic in the United States.

The patient of Simmons and Watson was a man aged 67, who had died from carcinoma of the esophagus. As he had been admitted to

Fig. 1.—The heart in the case of Simmons and Watson, showing distribution of calcification.

the Westminster Dispensary at London at a very advanced stage of the disease, the esophageal symptoms completely dominated the clinical picture, so that no evidence suggestive of a cardiac lesion was noticed. At necropsy, on opening the abdomen, a hard mass on palpation was felt through the diaphragm which later proved to be due to an extensive

massive calcification of a large portion of the heart. Watson says about the necropsy findings:

"The ossification possesses that surface of the heart which rests on the diaphragm; the center of it nearly corresponding with the septum ventriculorum. It extends from the basis to the very apex of the heart; is broadest in the middle, and branches out irregularly through the fleshy substance of both ventricles, over the greatest part of the auricle and for some way round the basis of the heart, following the course of the coronary vessels. On searching with the finger, I could nowhere perceive that it projected within the auricle or ventricle; so that it did not appear to have diminished their capacity."

It may also be of interest to hear Watson's theory on calcification. He says: "The measure of every morbid ossification will no doubt depend much on the abundance of creta in the habit. That it does abound in some, and that it is very deficient in other constitutions, we are fully convinced. . . . Ossification of the heart, so far as I have been able to observe, begins in the cellular membrane, under its investing coat, in specks or thin scales; and is at first superficial. It is analogous to the ossification in the the blood vessels, where the disease evidently begins in the cellular connecting medium between their coats, proceeding from within outwards, till at length the vessels are converted into complete bony tubes, such as we often find them. . . . It may not be improper to say, that flesh is ossified when the muscular texture is in any part totally destroyed, and its place usurped and occupied by earthy or cretacious matter, harder sometimes than bone itself." In other words, Watson thought that calcification takes place only in necrotic tisssue.

In 1809, Burns,[5] reporting a case of a thrombus in the left auricle, in a man with advanced coronary sclerosis, mentions that the flesh of the heart was "diseased with specks of bone."

Rokitansky,[6] 1849, briefly mentions a case of chronic cardiac lesion in which necropsy revealed advanced myocarditis with fatty degeneration. The apical portion of the heart showed evidence of calcification. Microscopic examination showed large number of calcium granules deposited between the partly destroyed muscle fibers.

Another case was published by Heschl[7] in 1861. A woman, aged 30, presented the classical picture of advanced Bright's disease associated with marked cardiac involvement. Necropsy revealed advanced myocardial degeneration, with deposition of calcium carbonate granules

5. Burns, A.: Disease of Heart, Edinburgh, 1809, p. 194.

6. Rokitansky: Beitrag zur Kenntniss der Verknoecherungsprozesse, Ztschr. d. k. k. Ges. d. Aertz in Wien. **1**:1, 1849.

7. Heschl: Teilweisl Verkreidung der Herzmuskulatur, Oesterr. Ztschr. f. prakt. Heilk. **7**:49, 1861.

within broken up heart muscle fibers. Heschl considers this case one of calcium metastasis as described by Virchow, notwithstanding the absence of any bone destructive process which might have caused an overloading of the blood with calcium salts. The advanced renal involvement appeared to him sufficient justification for his conclusions.

Coats,[8] in 1872, cites two cases of myocardial calcification. The first patient was a man brought to the hospital in a dying condition. He "evidently showed chronic bronchitis and emphysema with a possible syphilitic taint." Necropsy revealed a small pericardial effusion, extensive fatty degeneration of the heart and calcification of the apical portion of the left ventricle. The calcium was deposited in the form of minute granules within the muscle fibers.

His second case was a patient with relapsing fever followed by pyemia. Necropsy findings consisted of multiple abscesses in various organs, marked degenerative changes in the myocardium with areas of focal necrosis, the latter presenting numerous calcium phosphate deposits in the form of granules and plaques.

Coats also mentions that during his visit to Germany in 1870, he was shown by Dr. Koester at Wuerzburg, a heart, the myocardium of which was impregnated with lime deposits in fine granular form. He fails to give any details, nor has a report of this case ever been published.

Recklinghausen,[9] in 1883, says briefly that he has seen cases of calcification of the myocardium similar to those published by Coats, but he fails to give any further data.

Roth's [10] case, published in 1884, was a man aged 29, suffering from chronic traumatic osteomyelitis of the left hand followed by sepsis, associated with clinical evidence of marked renal involvement. Necropsy showed calcification in the heart wall, the kidneys and the stomach. Within the heart the calcium was scattered mainly throughout the ventricles in the form of fine granules deposited in degenerated muscle fibers. There was marked fatty degeneration. Muscle fibers presenting evidence of fatty degeneration did not, however, show any calcification.

In the kidneys the calcium was found mainly in the glomeruli, to a lesser degree also in the canaliculi.

In the stomach the calcium deposits were confined to the interstitial tissue of the mucosa. The glandular elements were not involved.

On the strength of the above findings, the case was considered by Roth one of calcium metastasis.

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8. Coats: Two Cases of Calcareous Infiltration of Muscle Fibers of the Heart, Glasgow M. J. **4**:433, 1872.

9. von Recklinghausen: Handb. d. allg. Path. d. Kreisl. u. d. Ernaehrung. 1883, p. 302.

10. Roth, M.: Ueber Metastasen von Kalk, Fett und Kohlenstaub, Kor. Bl. f. Schweizer Aerzte; **9**:226, 1884.

Jacobsthal,[11] in 1890, reports the case of a girl aged 3 weeks, who was markedly underdeveloped and icteric, in whom necropsy revealed evidence of an extensive, diffuse interstitial myocarditis associated with calcification of the anterior papillary muscle of the right ventricle.

Askanazy's [12] case, briefly mentioned in his work published in 1901, was a woman, aged 36, presenting the clinical picture of chronic endocarditis. Necropsy showed marked cardiac hypertrophy, calcification of coronary vessels, advanced myocarditis, irregular calcification within the wall of the left ventricle.

Langerhans' [13] publication (1902) contains a brief mention of a case of chronic lead poisoning, which at necropsy revealed marked calcification of the ventricles. No further data are given.

Rudis-Jicinsky's [14] paper on "Calcification of the Heart" could not be obtained.

Liebscher's [15] patient, in 1902, was a woman, aged 26, suffering from chronic pulmonary tuberculosis, chronic nephritis and cardiac insufficiency. Necropsy showed advanced myocarditis with small calcium phosphate deposits scattered throughout the heart muscle, and calcification within the liver and spleen.

Of great interest is the next case published in 1906. The clinical side was described by Leyden,[16] the pathologic side by Lazarus and Davidsohn. The patient was a girl, aged 19 years. The onset of the disease was sudden with pain and swelling of the joints, sweating, and rise in temperature, giving the clinical picture of acute rheumatism. At the cardiac apex there was a systolic murmur. Later, paralysis of the abducens nerve developed and the patient vomited several times. Death took place a few days later. Necropsy revealed an extensive sarcoma of the dura mater associated with advanced diffuse destruction of the tabulae of the skull. The heart was free in the pericardium; epicardium smooth; heart of the size of a fist; valves normal; the lining of the left auricle was hardened and covered with white calcareous plaques. There was extensive calcification also in the lung, kidneys and stomach. Microscopic examination showed that the calcifying changes

11. Jacobsthal: Verkalkung v. Herzmuskelfasern bei einem Kinde, Virchows Arch f. path. Anat. **159**:361, 1900.

12. Askanazy: Ueber Kalkmetastase und progressive Knoshenatrophy, Festschr. z. Feier d. 60. Geburtst. v. M. Jaffe, 1901, p. 187.

13. Langerhans: Grundriss der Allg. Path. und Pathol. Anat., Berlin, 1902, p. 419.

14. Rudis-Jicinsky: On Calcification of the Heart, J. West. Surg. Ass. Det., 1901, p. 37.

15. Liebscher: Ueber Herzmuskelverkalkung, Prag. med. Wchnschr. **27**:180-195, 1902.

16. Leyden and Davidsohn: Hirnhautsarkom mit zahlreichen Kalkmetastasen i. Herzen, Deutsch. med. Wchnschr. **32**:601, 1906; Ztschr. f. klin. Med. **60**:314, 1906.

were confined to the endocardium, while the myocardium and epicardium appeared normal.

The authors considered the case one of calcium metastasis in the sense of Virchow, and thought that in such cases lungs, kidneys and stomach form places of predilection for the deposition of calcium on account of their abundance in oxygen and acids.

Topham,[17] in 1906, reports a case of bone formation in the myocardium in a man, aged 71, who gave the clinical picture of chronic cardiac insufficiency, and in whom necropsy revealed evidence of advanced myocarditis with fatty degeneration, and two big pieces of bone in the anterior and posterior portions of the heart muscle.

At the meeting of the German Pathologic Society in 1907, Hedinger [18] reported two cases. The first one was a boy aged 15 years, suffering from chronic appendicitis followed by sepsis. Necropsy showed, besides the usual multiple abscesses in various organs, a large number of areas of focal necrosis within the wall of both ventricles mainly, associated with calcium deposits within the necrotic tissue.

Hedinger's second case was a man, aged 43, giving the clinical picture of chronic nephritis with marked cardiac involvement. Calcification was found to be extensive within the wall of both ventricles, the calcium being deposited within broken up muscle fibers. There was marked fatty degeneration around the calcified areas.

Hedinger explains the calcification process in his two cases on the basis of myocardial degeneration, being justified in doing so, he thinks, in view of the fact, that on careful microscopic examination he had found besides the calcified areas, numerous necrotic foci which were not calcified yet. The infrequency of published observations on myocardial calcification he explains by asserting that the fine calcified foci may quite often be overlooked at necropsy or be mistaken for something else.

In discussing Hedinger's paper, Roessle [19] and Fischer [20] report on similar findings. Roessle's case was a woman of middle age, who had died from uremia and in whom necropsy revealed findings closely similar to those described by Hedinger, the calcification being secondary to chronic myocarditis. Fischer's case was an infant, aged several weeks, presenting during lifetime evidence of marked cardiovascular disturbance. Necropsy showed advanced endocarditis and myocarditis with fatty degeneration. Calcified foci were scattered throughout the entire heart muscle and were most dense in the papillary muscles.

17. Topham: Bone Formation in the Heart, Brit. M. J. **2**:953 (Oct. 13) 1906.
18. Hedinger: Ueber Herzverkalkung, Verhandl. d. deutsch. path. Gesellsch. **10**:295, 1907-1908.
19. Roessle: Verhandl. d. deutsch. path. Gesellsch. **10**:303, 1907-1908.
20. Fischer: Verhandl. d. deutsch. path. Gesellsch. **10**:228, 1907-1908.

Wiechert,[21] in 1907, reported the case of a man, aged 48, who three days after eating fish had developed the clinical picture of sepsis and had died twenty days later. The case proved to be one of *B. paratyphosus* infection. On cross section, one found at the basal portion of the left ventricle the myocardium studded with small, pinhead sized, yellowish-gray, hard nodules which later on proved to be due to calcium phosphate deposits within necrotic muscle fibers. Besides the heart, calcification was found within the kidney, especially within the canaliculi and glomeruli. Wiechert considers the calcifying process in his case as secondary to myocardial degeneration of bacterial origin.

In 1909, Siebenmann [22] reported a case of a man, aged 36, who had suffered from advanced osteomalacia with extensive cystic degeneration of the long bones, chronic nephritis and cardiac insufficiency. Extensive calcification was found in this instance in the heart, kidneys, lung and liver. Within the wall of the left ventricle calcium phosphate was deposited in the form of fine granules as well as in the form of plaques in degenerated heart muscle fibers mainly, to a lesser degree also in the interstitial tissue, being most abundant around the vessels suggesting, according to the author, the probability that the calcium had been brought in by the blood stream. In the kidneys, the calcium was seen mainly within the canaliculi and the glomeruli, within the lung in the elastic tissue especially, within the liver in the middle portions of the acini. Siebenmann considers the case one of plain calciummetastasis in the sense of Virchow, being secondary to the bone dissolving osteomalacic process.

Hart's [23] case, published in the same year, is a woman, aged 24, with the clinical diagnosis of hereditary syphilis. The heart, on necropsy, presented evidence of fatty degeneration and a large number of necrotic foci, the latter containing calcium deposits in fine granular form. The calcification was confined strictly to the necrotic muscle fibers, the healthy muscle fibers being free from calcium deposits. Hart thinks that there is a definite relationship between the death of the cell and the deposition of calcium, and he believes that calcification does not take place in healthy tissue.

Of special interest and importance is the case of Versé,[24] in the year 1910. It presents a striking similarity to that of Leyden. A man, aged 25, had suffered from chronic myelogenous leukemia for a period of two

21. Wiechert, A.: Ueber einen Fall von Paratyphus B. mit Herzmuskelverkalkung, Inaugural Dissertation, Marburg, 1907.

22. Siebenmann, F.: Ueber Verkalkung der Herzmuskulatur. Inaugural Dissertation, Basel, 1909.

23. Hart, C.: Die Hermuskelverkalkung, Frankfurter Ztschr. f. Pathol. **3**:706, 1909.

24. Versé: Ueber ausgedehnte Verkalkg. d. Lunge, Lungenvene u. d. linken Vorhofs bei chron. myelog. Leukaemie; Verhandl. d. deutsch. path. Gesellsch. **14**:281, 1910.

and one-half years, presenting at times a clinical picture suggestive somewhat of acute rheumatism. Calcification was found to be present in the heart, the lungs and kidneys. In the heart, the calcifying process was confined exactly as in Leyden's case, to the endocardium and the subendocardial connective tissue of the left auricle. The other layers of the heart wall presented no abnormality. The accumulation of the calcium in the lung and kidneys was of the type described in some of the previous cases. Here again calcium in fine granular form was found mainly in the canaliculi and glomeruli of the kidneys, and in the elastic tissue of the lung, the elastic tissue "evidently being a place of predilection." Versé considers his case one of true calcium metastasis. The large amount of calcium salts made free by the leukemic process overloaded the circulation, the overload being deposited in the organs before mentioned. The fact that the calcification process in the auricles was confined to the endocardium, while the other parts of the heart wall were free from any changes, in other words, that the interior of the auricles practically was lined with calcium, suggests the probability that the calcium was taken up by the endocardium directly from the contents of the auricles, in other words, that the endocardial lining of the auricles was impregnated with calcium salts. Versé therefore concludes that the term "calcium metastasis" is, for his case at least, not a quite correct one, but that "heteroplastic calcium impregnation" would be a more proper designation of the process involved.

The findings in Pappenheimer's [25] case, concern a man, aged 21, in whom chronic sepsis had developed after an operation for gangrenous appendicitis. Necropsy revealed suppurative pyelophlebitis, thrombosis of the portal vein, multiple abscesses in various organs, and numerous areas of focal necrosis within the myocardium of the left ventricle mainly. Calcification was present in the left ventricle, the liver, lung, and kidneys. In the heart the calcifying process was confined strictly to the areas of focal necrosis where calcium phosphate was seen deposited in the form of fine granules within greatly degenerated muscle fibers, while healthy muscle fibers failed to present any calcification. There was no sign of inflammation, so that the lesion is definitely on a noninflammatory basis. The case, according to Pappenheimer, is one of toxic necrosis of heart muscle fiber followed by calcium deposits. Fatty degeneration, though present, did not seem to have any definite relation to calcification.

Tilp,[26] in 1912, describes the findings in a man, aged 28, who had been suffering from bronchiectases for two years. Gradually an empyema of the left side of the chest developed, for which an operation was done.

25. Pappenheimer, A.: Calcification of the Heart Muscle Fibers, Proc. New York Path. Soc. **10**:129, 1910.

26. Tilp: Herdfoermige Verkalkung des Myocardium bei Sublimatvergiftung, Verhandl. d. deutsch. path. Gesellsch. **15**:471, 1912.

This was followed by an attempt on the part of the patient to commit suicide by drinking 40 c.c. of a 5 per cent. solution of bichlorid of mercury. This again was followed by aneuria, icterus, diarrhea, cold sweats, coma, and death on the fifth day. Necropsy revealed within the myocardium of the left ventricle, especially in the region near the cardiac apex, numerous areas of focal necrosis containing calcium deposits. The calcification similar to the findings in Pappenheimer's case, was strictly confined to the necrotic heart muscle fibers. The kidneys presented the classical picture of "sublimatniere" (sublimate kidney) with calcium infarcts. Tilp points out that the myocardial calcification in this case is something very unusual, in view of the fact that in experimental "sublimatniere" with calcium infarcts in rabbits myocardial calcification has never been encountered.

The next case, published in the same year by Oppenheimer,[27] is of extreme interest and at the same time quite puzzling. A man, aged 44, presenting the clinical picture of mitral stenosis with auricular fibrillation, showed at necropsy an extensive calcification of the inner coat of the left auricle proper, so that the whole of the latter, except the auricular appendix and the interauricular septum, felt like a bony plate. Microscopic examination revealed that a portion of this plate was undergoing an osteogenetic process.

As to the further pathologic details in this case Oppenheimer says: "Only three blocks of tissue from the hard left auricular wall were sectioned, and in one of these we encountered an area undergoing ossification. This area presents both calcified and noncalcified osteoid tissue. The hard plate in the left auricular wall consists of hyaline degenerated connective tissue much of which is calcified. The lime deposit is distributed throughout the inner coat of the left auricular chamber and the inner coat only, leaving the striated muscle untouched. For the most part it is in the shape of scattered granules and plaques bordered by coarse granules; but also, though more rarely, it is in the form of nodules possibly representing calcified atheromatous patches. . . . There was fat present throughout most of the section, but not much in the calcified areas, so that no relation between the deposit of lime and a previous infiltration of fat is indicated. The test for amyloid proved negative.

"Though we believe that the deposit of lime was conditioned by the local hyaline degeneration of the cardiac tissue, we must admit the possibility that an increased calcium content of the circulating body fluids may account for the lime deposits in the left auricle. We grant this

27. Oppenheimer, B. S.: Calcification and Osteogenic Changes of Left Auricle in a Case of Auricular Fibrillation, Proc. New York Path. Soc. **12**:213, 1912.

possibility because we were unable to exclude it by an examination of the excretions during life or of the bones at necropsy. On the other hand, in our case sections of lung, kidney, liver and spleen, free of lime salts as they are, indicate that calcium metastasis played no rôle."

At the first sight it would seem that the findings in Oppenheimer's case may nullify our reasoning as expressed here, with regard to calcium impregnation of the endocardium of the left auricle in cases of calcium metastasis. It must be admitted that one might very easily be induced to consider this case as one of calcium metastasis. And yet it is not so, because the endocardial calcification process in calcium metastasis consists in the precipitation of calcium salts into the endocardial layers of an otherwise perfectly normal heart wall in patients with evidence of extensive bone destructive processes. Different are the conditions in Oppenheimer's case. On one hand, there is no evidence of any bone destructive process which could account for a possible overloading of the body fluids with calcium salts; on the other hand, satisfactory explanation for the calcifying process is given by the presence of hyaline degeneration associated with deposit of fat not infrequently observed in beginning atherosclerosis as found in the blood vessels, in cardiac valves, much less frequently, according to Kaufmann, in the endocardium of the auricle, sometimes also of the ventricle, a process which is followed rather frequently by calcification, as hyalinized connective tissue attracts calcium salts quite readily. Oppenheimer therefore was justified in not classifying his case as one of calcium metastasis, but explaining the calcifying process on a retrogressive basis. This case, therefore, will be placed in our classification table into the column of "myocarditis" with the understanding that the retrogressive changes present are of the foregoing type specified.

Krayn,[28] in 1914, wrote an inaugural dissertation on "Herzverkalkung." His case is a woman, aged 54, presenting the clinical picture of a double mitral lesion, associated with marked cardiac hypertrophy and dilatation, decompensation and renal insufficiency. Small calcified foci were found scattered throughout the entire myocardium. The calcium was deposited within broken up heart muscle fibers either in the form of fine calcium carbonate granules or small plaques. Healthy muscle fibers failed to show any calcification. Evidence of fatty degeneration was present in calcified and noncalcified fibers. The kidneys were of the granular contracted type. The findings in this case are explained by Krayn on the basis of interference with the calcium excretion in the kidneys, followed by secondary calcium deposits within the necrotic areas of the myocardium.

28. Krayn, M.: Ueber Herzmuskelverkalkung. Inaugural Dissertation, Heidelberg, 1914.

In 1915, Bergamowitch [29] published two cases of calcification of the heart muscle. No further data can be given, as the original article could not be obtained.

REPORT OF CASE

My own case was a man, aged 74, a Russian, married, peddler by occupation, who was admitted to the Montefiore Home, April 30, 1917, where he died July 11, 1917. His family history was negative. His personal history showed he was an excessive smoker; he did not drink, he was a strenuous worker all his life; he had no children and his wife had no miscarriages. The previous history: Syphilis was denied; the patient had had gonorrhea at 18; otherwise the history was negative.

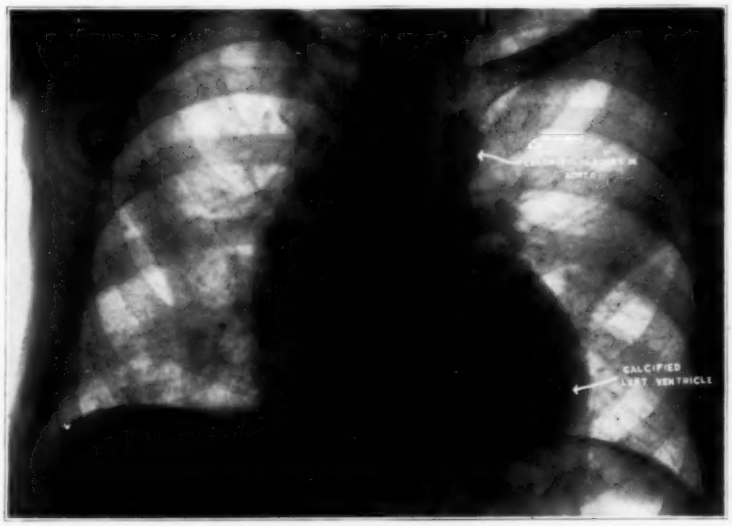

Fig. 2.—Postero-anterior roentgenogram of the chest of my patient, taken intra vitam, showing the ring-like shadow within apical portion of the heart, and the oval shaped shadow within the bulbus aorta.

Present Illness.—Sudden onset eighteen months ago, with loss of consciousness and speech, stupor, involuntary urination and defecation. No convulsions. He was confined to bed for two months, and the recovery was gradual. Since then he had a chronic cough, expectoration, swelling of the feet and dyspnea on slight exertion.

Physical Examination.—Evidence of chronic emphysema, advanced arteriosclerosis, moderate cardiac insufficiency and bilateral inguinal hernia were present.

Roentgenologic examination of the chest was made on June 14. Fluoroscopy revealed marked diffuse fibrosis throughout the median portions of both lungs; hyperaeration of basal portions, low position of diaphragm, poor diaphragmatic excursions; moderate enlargement of heart to left; very superficial left ventricular contractions; increased bulging of aortic arch. The roentgenogram showed a fine, ring-like shadow, about 3.5 cm. at its widest diameter, occupying

29. Bergamowitch: Two Cases of Calcification of the Heart, Sibirsk-Vrach, Tomsk, 1915.

the apical portion of the heart (Fig. 2). There were other oval shaped shadows within the aortic arch. Roentgenologic conclusions were: chronic lung fibrosis; moderate cardiac enlargement; suggestion of myocardial involvement; calcium plaques in wall of aortic arch; suggestion of calcification within the shadow of the cardiac apex, either in the pericardium or myocardium.

Roentgenologic reexamination was made on June 17. Plates of the heart were taken with the aid of small diaphragm intensifying screens and instantaneous exposures, with the patient in various postures. The entire calcified area in the region of the left ventricle could be demonstrated very definitely. From the various plates taken at various angles it could be well seen that the calcifying process solidly involved the entire apical portion of the heart (Fig. 3).

The patient died several weeks later from an incarcerated hernia.

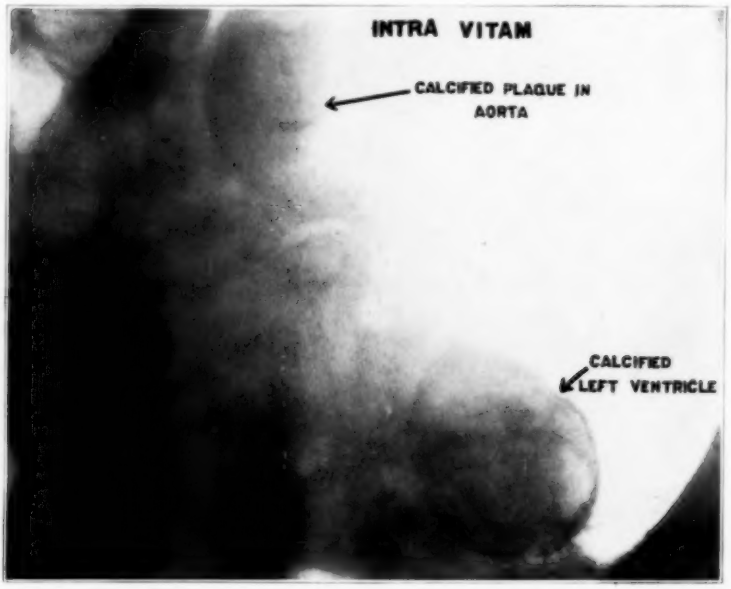

Fig. 3.—Intra vitam roentgenogram of the cardiac region taken with the patient in an oblique posture, showing the entire calcified area within the apical portion of the heart.

Necropsy.—The heart weighed 550 gm. and was somewhat enlarged; on palpation through the pericardium a very hard mass was felt over the entire apical surface; the pericardium was adherent by fibrous tissue over the anterior and left surfaces. Left auricle: the endocardium was white and milky; in the anterior leaflet of the mitral valve was a small, hard calcified plaque. Left ventricle: in its lower half was a cup shaped area of complete calcification (Fig. 4), extending 5 cm. from the apex on the anterior surface, 3.5 cm. on the diaphragmatic surface and 4 cm. on the interventricular surface. The ventricular aspect of this calcified cup was irregular and marked by shallow depressions and elevations. Otherwise, it was evidently covered by smooth endocardium. The external aspect was covered by thin layers of fibrous pericardium. The coronary arteries were thickened, slightly tortuous, calcified to veritable pipe stems; the lumen of the left coronary was almost completely occluded, leaving a passage about as thin as a hair. Aorta:

a number of calcified plaques were in its ascending and transverse portions. Microscopic examination showed that within the calcified area very little muscular tissue was in evidence. The heart muscle cells were broken up by masses of dense scar tissue. The calcium (phosphate) was found deposited in the form of irregular plaques.

We have here, therefore, a case in which calcium has been deposited in large quantities within the necrosed apical portion of the heart following a gradually complete obliteration of the left coronary artery. It is interesting to note that here, as in the case of Simmons and Watson, the patient was able to carry on a moderately bearable life notwithstanding the fact that a large portion of the left ventricle had been practically put out of commission.

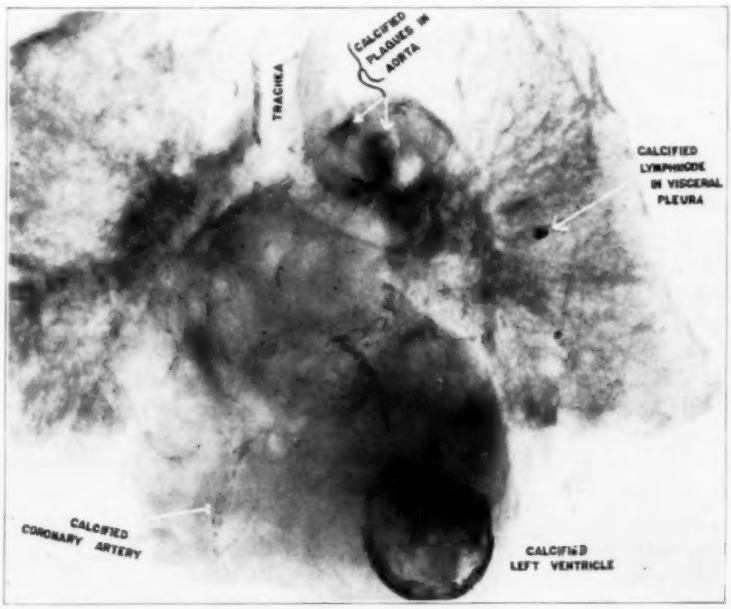

Fig. 4.—Roentgenogram of the necropsy specimen.

ROENTGENOLOGIC ASPECT OF CALCIFICATION OF THE HEART

Roentgenologic literature on calcification of the heart and its demonstration intra vitam is extremely scanty. There are only two previous instances on record in which a roentgen-ray diagnosis of calcification in the heart itself was made during lifetime, namely, the cases of Groedel [30] and Le Wald.[31] Unfortunately, however, in neither one of those cases

30. Groedel, F. M.: Erste Mitteilung ueber die Differenzierung einzelner Herzhoehlen im Roentgenbilde und den Nachweis von Kalkschatten i. d. Herzsilhouette intra vitam. Fortschr. a. d. Geb. d. Röentgenstrahlen **16**:337, 1911.

31. Le Wald, L.: Discussing this Paper at the German Medical Society, New York, Feb. 4, 1924.

was a necropsy obtained, so that the final diagnosis can only be surmised. Our case, therefore, is the first one in which calcification of the heart itself was demonstrated roentgenologically intra vitam, was differentiated from calcification of the pericardium and in which the roentgenologic diagnosis was confirmed by necropsy. The cases published by Simmonds [32] concern roentgenograms of necropsy specimens.

In contrast to myocardial calcification, roentgenologic literature on pericardial calcification is quite abundant, as is shown by the publications of Rieder,[33] Schwarz,[34] Klason,[35] Mueller,[36] Weil,[37] Case [38] and others. A similar case with necropsy findings was demonstrated by me [39] several years ago. Though it is not the purpose of this paper to deal with roentgen-ray findings in calcifying pericarditis, this subject must briefly be touched on here for differential diagnostic purposes.

In cases where the calcifying process involves diffusely the entire pericardial sac, the calcified plaques within the anterior and posterior portions of the pericardium may or may not be shown on the usual front view plates, while the tangentially increased diameter of the calcified plaques along the lateral aspects of the heart will document themselves in the form of dense, bandlike shadows running just outside of and parallel to the heart shadow proper. In such cases a roentgenologic diagnosis of pericardial calcification is justified. In cases where only the anterior or posterior portion of the pericardial sac is calcified, the usual front view plates may present round, or ringlike or diffuse shadows within the heart shadow proper. In such instances and if front view plates only have been taken, one is not justified in making a definite diagnosis of pericardial calcification, because there is in the appearance of such shadows nothing which would differentiate them from those cast by myocardial calcification. Yet one may, even in such cases, arrive at a certain degree of differentiation between these two conditions by taking plates with the patient in various postures. If the case is one of pericardial calcification one may thus obtain a certain view in which the pericardial plaques are struck by the roentgen-ray tangentially, and thus present themselves as the bandlike dense shadows just outside of the

32. Simmonds: Ueber den Nachweis von Verkalkungen am Herzen durch das Roentgenverfahren, Fortschr. a. d. Geb. d. Roentgenstrahlen **12**:371, 1908.
33. Rieder: Panzerherz, Fortschr. a. d. Geb. d. Roentgenstrahlen **20**:50, 1913.
34. Schwarz: Die Roentgenuntersuchungen des Herzens und der grossen Gefaesse, Leipzig, 1911.
35. Klason: Pericarditis calculosa und Herzverkalkung, Acta Radiol. **1**:162, 1921.
36. Mueller: Perikardiale Verkalkung, Fortschr. a. d. Geb. d. Roentgenstrahlen, **25**:231, 1918.
37. Weil: Panzerherzund Pick'sche Lebercirrhose; Fortschr. a. d. Geb. d. Roentgenstrahlen, **23**:489, 1916.
38. Case, J. T.: Pericarditis Calculosa, J. A. M. A. **80**:236 (Jan. 27) 1923.
39. Scholz, T.: New York Physicians Association, March 6, 1919.

heart area proper, as described above. Or one may, like in my case, by means of the various views, succeed in demonstrating that the calcifying process involves the heart proper. It might therefore be not quite advisable and even prove misleading to interpret abnormal shadows within the heart area somewhat indiscriminately at one time as myocardial, at another time as pericardial calcification without having a justification, in form of necropsy control, for so doing.

Calcification within the bulbus aorta can be diagnosed by roentgen ray very easily. Even calcified plaques within the descending aorta may be visualized by taking plates with the patient in an oblique posture. They present themselves on the plate as narrow, somewhat lengthy shadows running longitudinally just in front of the spine. Here too, apparently only those plaques are demonstrable which happen to be struck by the roentgen ray tangentially, whereby the diameter of the individual plaque is increased.

Large calcified areas within the heart muscle itself, as in my case, may be visualized by roentgen ray intra vitam. The use of double intensifying screens, small diaphragms, various postures of the patient, rapid, but at the same time sufficient, exposures will aid in obtaining desirable results. Small, fine calcified foci, for obvious reasons, cannot be demonstrated during life time with our present machinery. Possibly we will be able to do so after a further development of the roentgen-ray technic.

In necropsy specimens one is able to demonstrate by means of the roentgen ray the most minute calcified foci within the heart as well as within practically any other part of the body, as Simmonds has shown and as my own experience indicates. In the heart, for instance, it is advisable to slice up the specimen, to spread it apart and then to place it flatly on the plate. Soft tubes and slow developer should be used. As a quick and accurate localizer of small calcified areas or of any other small, localized gross pathologic changes such as produce roentgenographically sufficient differentiation of tissue densities, the use of the roentgen ray ought to be considered of very great importance for the pathologist. It is to be regretted that the roentgen ray is not universally used yet for such purposes. The results of my necropsy roentgen-ray investigations, which had been carried out on a large scale during the years from 1914 to 1920, which work will soon be published, tend to show that if roentgen ray was employed during necropsy work systematically, calcification of the heart and some other supposedly very rare conditions would be found to be more frequent than is believed at the present time. The importance of the roentgen ray for gross pathologic studies is so great that there is no doubt that every department of pathology will have a complete roentgen-ray outfit of its own, once pathologists realize what possibilities may be opened up by this new aid.

CLASSIFICATION OF CASES OF MYOCARDIAL CALCIFICATION

Going very briefly over the cases enumerated in Table 1, taking as a guide the pathologic conditions found at necropsy, omitting those cases in which the authors failed to give satisfactory data, and ignoring for the present the finer points pertaining to myocardial calcification, one may for practical purposes be justified in classifying the cases so far published in the manner given in Table 2.

The first column contains all those cases which have in common one and the same stigma of myocardial degeneration, namely, myocarditis. This process may be diffuse or localized. In the vast majority of the cases it is expressly pointed out by the authors that the calcium containing muscle fibers were broken up or entirely destroyed. In some other instances microscopic examinations have not been made at all, or evidently were not made carefully enough. We then have to be satisfied with the macroscopic necropsy evidence of a retrogressive metamorphosis within the myocardium. In none of the cases where careful microscopic examinations were made, has it been found that calcification has taken place in healthy muscle fibers. Of extreme interest in this connection are the findings in the case of Jacobsthal [11] (Table 1, No. 10) where the myocarditic process, as well as the calcifying changes, were strictly confined to the anterior papillary muscle of the right ventricle. The primary cause of the myocarditis is of secondary importance. The calcifying process in this type of case consists of deposition of fine granules of calcium, usually calcium phosphate, within the destroyed heart muscle fibers. As these calcium granules gradually coalesce, forming smaller and larger plaques, the calcifying process may also involve the neighboring interstitial tissue. Occasionally, an osteogenetic process may develop within the calcification area and real bone may be formed similar to that found in the cases of Topham [17] and Oppenheimer,[27] for reasons not definitely known yet.

Into the second column have been placed the cases in which, owing to obliteration of the coronary artery, usually the left one, a large area of the heart wall has been rendered useless, has become dead tissue and then was gradually impregnated with calcium salts. Here the calcifying process gradually takes on a massive solid form involving a large area, and all the elements of the heart wall. It may be worth while noting that this apparent elimination of so large a portion of the heart muscle causes very little distress to the patient unless the conductive system of the heart happens to be interfered with by the calcifying process.

The third column contains the cases of chronic sepsis in which the septic process had caused, besides the usual multiple abscesses in various organs, numerous areas of focal necrosis within the myocardium. In

these instances the calcifying process is strictly confined to the areas of focal necrosis, while the other healthy portions of the heart muscle fail to present any calcium deposits. The causative factors of the septic process and possible accidental combination with another causa nocens are of no importance for the consideration of our subject of myocardial calcification. Thus in Tilp's [26] case one has to eliminate the bichlorid poisoning (in the patient's attempt to seek relief from his septic disease by committing suicide) as the primary cause of the myocardial calcification. Tilp's surprise to find in a case of bichlorid poisoning a combination of a classical "sublimatniere" with myocardial calcification, something never observed before, was therefore not quite justified, because the bichlorid poisoning had nothing to do with the calcification within the heart wall, which would have been seen at the necropsy just as distinctly without the suicide attempt. Here, too, the calcium is deposited in the form of fine granules within the destroyed muscle fibers only. These granules may gradually coalesce, forming plaques. On cross section through the involved heart muscle, one sees macroscopically small areas of pin-head size and even more minute ones, yellowish-gray, slightly prominent and somewhat hard to touch.

Of special interest is column four, representing the cases of so-called calcium metastasis of Virchow.[1] The latter published, in 1855, a series of five cases which clinically presented the picture of an extensive bone destructive lesion, be it diffuse bone carcinomatosis, or sarcomatosis, or oseomalacia, etc., superimposed to a certain degree by a second clinical picture somewhat suggestive of acute rheumatism. Necropsy examination showed, besides the bone destructive process, extensive calcium deposits within the lung, the kidneys and the stomach. In the lung, the elastic tissue was the place of predilection for the calcium deposits, in the kidneys and the stomach the epithelial elements. It would be too lengthy to go into the details of the interesting description of the findings given by Virchow. Suffice it to say that Virchow thought that the large amounts of calcium salts made free by the diffuse bone destructive processes overloaded the circulation to such an extent that the usual provisions for calcium excretion became inadequate to their task, the overload of calcium salts being then deposited, or rather precipitated, directly within the otherwise healthy organs before mentioned. There were no calcium deposits in the heart. If one accepts the view that the cases of Virchow are classical instances of calcium metastasis, one must place in our series of heart calcification the cases of Leyden [16] and Versé [24] into the same category. Here, too, we have a bone destructive process, a clinical picture of the latter finally superimposed to a certain extent by another one somewhat suggestive of acute rheumatism, and finally calcium deposits within kidneys, lung and stomach in one case and

TABLE 1.—*A Brief Review of Clinical, Pathologic and Anatomic Findings in all the Published Cases*

No.	Year	Author	Patient's Sex*	Patient's Age, Years	Clinical Features	Necropsy Findings: General Condition of Heart	Necropsy Findings: Calcification: Heart	Kidneys	Lung	Stomach	Other Organs	Involved Elements of Heart
1	1708	Bordenave	♂	50	Chronic cardiac insufficiency	Advanced myocarditis, adhesive pericarditis	Massive calcification of right ventricle	—	—	—	—	
2	1783	Simmons and Watson	♂	67	Carcinoma of esophagus	Chronic myocarditis	Massive calcification along septum	—	—	—	—	All elements
3	1809	Burns	♂	..	Advanced arteriosclerosis, coronary sclerosis	Thrombosis of left auricle, calcification of coronary arteries, chronic myocarditis	Irregular massive calcification of left ventricle	—	—	—	—	
4	1849	Rokitansky	..	..	Chronic cardiac lesion	Advanced myocarditis, fatty degeneration	Calcium granules in apical portion	—	—	—	—	Destroyed muscle fibers only
5	1861	Heschl	♀	50	Advanced Bright's disease, cardiac insufficiency	Advanced myocarditis, degeneration	Diffuse in form of granules	—	—	—	—	Destroyed muscle fibers only
6	1872	Coats	♂	..	Chronic bronchitis, "syphilitic taint"	Pericardial effusion, extensive fatty degenration	Calcium granules in apical portion	—	—	—	—	Degenerated muscle fibers
7	1872	Coats	..	..	Relapsing fever sepsis	Chronic myocarditis, areas of focal necrosis	Calcification of areas of focal necrosis	—	—	—	—	
8	1870	Koester (mentioned by Coats)	..	..	.....	.....	Diffuse impregnation of myocardium with calcium granules	—	—	—	—	
9	1884	Roth	♂	29	Chronic osteomyelitis, sepsis, renal insufficiency	Chronic myocarditis, fatty degeneration	Calcium granules in ventricles mainly	Glomeruli and canaliculi	—	Mucosa	—	Degenerated muscle fibers
10	1890	Jacobsthal	..	3 weeks	Syphilis (?)	Localized interstitial myocarditis of anterior papillary muscle of right ventricle	Calcium granules in anterior papillary muscle of right ventricle	—	—	—	—	
11	1901	Askanazy	♀	36	Chronic endocarditis	Cardiac enlargement, calcification of coronary vessels; advanced myocarditis	Massive calcification within wall of left ventricle	—	—	—	—	All elements
12	1902	Langerhans	..	..	Chronic lead poisoning	.....	Ventricles	—	—	—	—	
13	1902	Liebscher	♀	26	Chronic pulmonary tuberculosis, chronic nephritis, cardiac insufficiency	Advanced myocarditis	Diffusely scattered calcified foci	—	—	—	Liver, spleen	Degenerated muscle fibers

14	1906	Leyden and Lazarus	♀	19	Sarcoma of dura with clinical picture suggestive of acute rheumatism	Normal myocardium and epicardium	Calcification of endocardium of auricles	Glomeruli and canaliculi	Elastic tissue mainly	Mucosa	—	Endocardium only
15	1906	Topham	♂	71	Chronic cardiac insufficiency	Advanced myocarditis, fatty degeneration	Bone plates in anterior and posterior heart wall	—	—	—	—	
16	1907	Hedinger	♂	15	Chronic appendicitis, sepsis	Areas of focal necrosis	Calcium deposits within areas of focal necrosis of both ventricles	—	—	—	—	
17	1907	Hedinger	♂	43	Chronic nephritis, cardiac insufficiency	Chronic myocarditis	Calcium granules within destroyed muscle fibers	—	—	—	—	Degenerated muscle fibers
18	1907	Roessle	♀	Middle age	Uremia	Chronic myocarditis	Diffuse calcium deposits	—	—	—	—	
19	1907	Fischer	..	Infant	Cardiovascular disturbance	Multiple valvular lesion, endocarditis, myocarditis, fatty degeneration	Diffuse calcium deposits, mainly in papillary muscles	—	—	—	—	
20	1907	Wiechert	♂	48	Paratyphus B. sepsis, renal insufficiency	Numerous areas of focal necrosis	Calcium deposits within areas of focal necrosis	Glomeruli and canaliculi mainly	—	—	—	Degenerated muscle fibers
21	1909	Siebenmann	♂	36	Advanced osteomalaria, chronic nephritis, cardiac insufficiency	Chronic myocarditis	Diffuse calcification in form of granules and plaques in left ventricle	Glomeruli and canaliculi mainly	Elastic tissue mainly	—	Liver	
22	1909	Hart	♀	24	Congenital syphilis	Fatty degeneration, numerous necrotic foci	Calcium in granules within destroyed muscle fibers	—	—	—	—	Degenerated muscle fibers
23	1909	Versé	♂	25	Chronic myelogenous leukemia with cystic bony destruction	Normal myocardium and epicardium	Endocardium of auricles impregnated with calcium	Glomeruli and canaliculi mainly	Elastic tissue mainly	—	—	Endocardium only
24	1910	Pappenheimer	♂	21	Gangrenous appendicitis, sepsis	Areas of focal necrosis	Calcium granules within areas of focal necrosis	Glomeruli and canaliculi mainly	Elastic tissue mainly	—	Liver	Degenerated muscle fibers only
25	1912	Tilp	♂	28	Bronchiectasis, empyema lung, chest, sepsis, bichlorid poisoning	Areas of focal necrosis	Calcium deposits within areas of focal necrosis	"Sublimatniere" with calcium infarcts	—	—	—	Degenerated muscle fibers only
26	1912	Oppenheimer	♂	44	Auricular fibrillation	Hyaline degeneration of endocard.	Calorific and beginning bone formation of endocard.	—	—	—	—	Endocardium only
27	1914	Krayn	♀	54	Mitral stenosis, cardiac and renal insufficiency	Chronic myocarditis	Calcium deposits within degenerated muscle fibers	—	—	—	—	Degenerated muscle fibers only
28	1915	Bergamowitch	..	..	.....	.....	.....	—	—	—	—	
29	1915	Bergamowitch	..	..	.....	.....	.....	—	—	—	—	
30	1924	Scholz	♂	74	Advanced arteriosclerosis	Advanced calcification of coronary arteries, diffuse myocarditis	Massive calcification of apex	—	—	—	—	All elements

* In this column, ♀ indicates female; ♂, male.

within the kidneys and lung in the other case, and within the endocardium of the auricles in both cases. The character of the calcium deposits corresponds to that described by Virchow. The calcification process in the endocardium of the auricles, though not present in Virchow's, but present in both Leyden's and Versé's case, also would fit very perfectly into the classical picture of calcium metastasis: the endocardium of an otherwise perfectly normal heart impregnated with calcium salts. One should bear in mind that in true calcium metastasis or rather "heteroplastic calcium impregnation" the calcifying process is produced by direct deposition of calcium salts from the calcium-oversaturated fluids into the adjacent but normal tissue elements. There must, therefore, be in the calcified organs themselves no pathologic changes which could

TABLE 2.—*Classification of Cases of Calcification of the Heart*

1	2	3	4 Calcium Metastasis		5
			(a) Pure Calcium Metastasis Involving Endocardium Only	(b) Combined with Myocarditis Causing Calcification of Myocardium	
Myocarditis	Obliteration of Coronary Arteries	Sepsis			Direct Extension from Calcifying Pericarditis
1. Bordenave 2. Simmons 3. Rokitansky 4. Heschl 5. Coats I 6. Jacobsthal 7. Liebscher 8. Topham 9. Hedinger II 10. Roessle 11. Fischer 12. Hart 13. Oppenheimer 14. Krayn	1. Burns 2. Askanazy 3. Scholz	1. Coats II 2. Hedinger I 3. Wiechert (Paratyphys B.) 4. Pappenheimer 5. Tilp (bichlorid poisoning)	1. Leyden (sarcoma of dura) 2. Versé (myelogenous leukemia)	1. Roth (chronic osteomyelitis) 2. Siebenmann (osteo-malaria)	1. Diemer 2. Obendorfer 3. MacFarland 4. Lucas

possibly account for the calcium deposits. If one applies this standard to the cases of Roth and Siebenmann, both of which are classified by the authors as instances of calcium metastasis, one must immediately admit that neither one of these cases can be considered as true calcium metastasis, so far as the myocardial calcification process is concerned; because in both instances necropsy revealed evidence of advanced myocarditis, which latter, per se, would fully account for calcium deposits. Furthermore, the type of calcification, in the form of fine granules within destroyed heart muscle fibers, is here quite different from that in Leyden's and Versé's cases in which the calcium directly impregnated the endocardium of the auricles. Roth's [10] and Siebenmann's [22] cases therefore belong, from the point of myocardial calcification, to the myocarditis cases of the first column, though it has to be admitted that from the point of their renal, gastric and pulmonary calcification, and also in view of the presence of an extensive bone destructive process,

they belong to the class of calcium metastasis. These latter classic features of calcium metastasis may, but must not necessarily, have aided in the production of calcium deposits within the degenerated myocardium in Roth's and Siebenmann's cases.

In covering the various types of calcification of the heart, one has to include the cases in which calcification of the myocardium has been produced by direct extension of the calcifying process in calculous pericarditis. Some of such instances, like the cases of Diemer,[40] Oberndorfer,[41] McFarland [42] and Lucas,[43] where the authors have furnished careful microscopic reports, have been collected in column five. These cases are of great importance in the consideration of the causative factors of our subject, because the microscopic sections reveal how the completely adherent calcified pericardium causes by direct pressure first atrophy of the epicardium, then this pressure atrophy is followed by deposition of fine calcium granules within the atrophied area; how these latter calcified areas again cause pressure atrophy of the adjacent heart muscle fibers, which again is followed by depositions of calcium granules within the broken up muscle fibers; and how this calcifying process gradually may extend deep into the myocardium, always selecting degenerated, never healthy, muscle fibers as steps in its gradually advancing invasion. These findings seem to be an additional proof for the belief that calcification of the heart never takes place in healthy tissue, except in calcium metastasis where it involves the endocardium only.

THEORIES ON CALCIFICATION OF THE HEART

All textbooks on pathology agree that calcification of the heart is a very rare condition. Aschoff [44] and Kaufmann [45] add that the calcification process, as a rule, is preceded by a regressive metamorphosis of the heart muscle fibers, except possibly where the process is part of a general calcium metastasis when it is associated with calcium deposits in the kidneys, stomach, lung and sometimes in ulcer of the liver. Adami [46] doubts whether calcification ever takes place in living tissue. He is inclined to believe that it occurs only in dead tissue. Even in cases of calcium metastasis, where calcium apparently is deposited in living tissue, careful

40. Diemer: Ztschr. f. Heilk. **20**:185, 1899.

41. Oberndorfer: München. med. Wchnschr. **53**:2081, 1906.

42. McFarland, J.: The Pathology and Pathogenesis of Pericarditis, J. A. M. A. **37**:1507 (Dec. 7) 1901.

43. Lucas: Pericardial Calcification, Brit. M. J. **2**:1404, 1907.

44. Aschoff: Pathol. Anatomie, Jena; G. Fischer, **2**:20, 1919.

45. Kaufmann: Lehrbuch d. Spez. Pathol. Anatomie; Berlin, G. Reimer, **1**: 35, 1911.

46. Adami and Nicholls: Principles of Pathology; Philadelphia, Lea & Febiger, 1911, **1**:930; **2**:154.

microscopic examinations, he thinks, tend to show that the calcifying process in such instances involves not the living cellular tissue but only the inanimate, intercellular parts of the living tissue. MacCallum [47] does not take any definite stand. According to his opinion there are so many still unsolved questions involved in the consideration of this subject, that no definite conclusions can be reached at the present time. According to Wells,[48] heteroplastic calcification never occurs in normal tissue, except perhaps in metastatic calcinosis.

Special studies in connection with the subject of calcification in general have been made by Aschoff,[49] Lichtwitz,[50] Gierke,[51] Goldthwait,[52] Erlich,[53] Schultze [54] and Wells.[55] These authors could not solve the problem, but came to the conclusion that many points, with regard to the causative factors of pathologic calcification, still remain obscure and unexplained, and that it would be of great interest and importance to study more minutely the normal calcification process, especially to find out which elements of the cartilage take up the calcium first. Wells calls attention to the interesting feature of the daily excretion of from 4 to 5 gm. of calcium carbonate by a laying hen, and to the investigations made as to the nature of the stimulus which causes a shell to be formed on a bird's egg. Here one may add the likewise interesting observation commonly made on farms that a certain injury may cause a hen to lose her ability of forming a shell around her egg, to lay eggs without a shell for a period of time, and finally to gradually regain her lost capacity of forming a calcium shell.

The nature of calcification in cases of the so-called calcium metastasis, like in the instances of Virchow,[1] Versé,[24] Leyden, Wiechert [21] and Roth,[10] has been dwelt on by Wells,[55] Askanazy,[12] Hofmeister,[56]

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47. MacCallum, W. G.: Textbook of Pathology; Philadelphia, W. B. Saunders Company, 1920, pp. 106 and 253.

48. Wells, H. G.: Chemical Pathology; Philadelphia, W. B. Saunders Company, 1920, p. 439.

49. Aschoff: Verkalkung; Ergebn. d. path. **8**:1, 1902.

50. Lichtwitz: Ueber d. Bedeutung d. Kolloide f. d. Konkrementbildung u. die Verkalkung; Deutsch. med. Wchnschr. **36**:704, 1910.

51. Gierke: Ueber Eisengehalt verkalkter Gewebe unter normalen u. pathol. Bedingungen; Virchows Arch. f. path. Anat. **167**:318, 1902.

52. Goldthwait; Painter; Osgood, and McCrudden: A Study of the Metabolism in Osteomalacia; Am. J. Physiol. **14**:389, 1905.

53. Erlich: Eisen impregnation and Kalk impregnation i. menschel. Geweben, insbesondere den elastischen Easern, Zentralbl. f. path. **17**:177, 1906.

54. Schultze: Die Verkalkung; Ergebn. d. allg. path. **14**:707, 1910.

55. Wells, H. G.: Calcification and Ossification, Arch. Int. Med. **7**:721 (June) 1911; Pathological Calcification, J. M. Res. **14**:491, 1906; Wells and Benson: Studies on Calcification, J. M. Res. **12**:15, 1907; Wells and Mitchell: Studies on Calcification and Ossification, J. M. Res. **22**:501, 1906.

56. Hofmeister: Ueber Ablagerung u. Resorption v. Kalksalzen i. d. Geweben; Ergebn. d. Physiol. **10**:429, 1910.

Huebschmann [57] and Schmidt.[58] They explain the calcium deposits in the kidneys, lung and stomach of such cases by the fact that in these organs acids are excreted into cavities which leave the fluids in the substances of these parts correspondingly alkaline. This increase in the alkalinity of the fluids makes the calcium salts decidely less soluble, so that in instances where for some reasons the total amount of free calcium salts in the body fluids is greatly increased, calcification in these organs may take place under certain conditions. Such calcifying process may possibly be aided by a nephritis which latter, according to Schmidt,[58] may cause blood changes which tend to diminish the solubility of the calcium salts. He succeeded in such a case in demonstrating precipitation of calcium in the blood. Erbe [59] found increased amounts of calcium in the blood in some cases of nephritis.

Thorel,[60] in reviewing the literature on myocardial calcification, is of the opinion that the subject of calcification of the heart as well as calcium metastasis is so little cleared up that it is impossible to arrive at any definite conclusions. He somewhat doubts the existence of metastatic calcinosis, as does also Askanazy [12] and Kockel.[61]

The question of heteroplastic bone formation in general, and of bone formation within calcified areas of the heart and arteries, as well as of other parts of the body, has been made the subject of investigations by Porscharisky,[62] Buerger and Oppenheimer,[63] Harvey,[64] Rosenstein,[65] Rohmer,[66] Maximow [67] and others. Of special interest are the observations made with regard to the changes which, under certain circumstances, may gradually take place within the cells constituting the calcified mass and which may slowly lead to the formation of blood vessels. This tends to show that the ultimate cause of heteroplastic ossification,

57. Huebschmann: Zur Histologie d. Kalkmetastase, Zentralbl. f. Allg. Path. u. Path. Anat. **19**:737, 1908.

58. Schmidt: Kalkmetastase u. Kalkgicht, Arb. a. d. Path. Inst. Marburg, 1913.

59. Erbe: Ueber die Zusammensetzung d. Blutes; Zentralbl. f. klin. med. **1**:441, 1903.

60. Thorel: Pathol. Krauslauforgane; Ergebn. d. Pathol. **2**:284, 1910.

61. Kockel: Deutsch. Arch. f. klin. med. **64**:332, 1899.

62. Porscharisky: Ueber heteroplastische Knochenneubildung; Beitr. z. path. Anat. u. z. allg. Path. **38**:135, 1905.

63. Buerger and Oppenheimer: Bone Formation in Sclerotic Arteries, J. Exper. Med. **10**:354, 1908.

64. Harvey: Experimental Bone formation in Arteries, J. M. Res. **17**:25, 1907.

65. Rosenstein: Ueber Knochen. und Knorpelbildung i. Herzklappen, Virchows Arch. f. path. Anat. **162**:100, 1900.

66. Rohmer: Ueber Knockenbildung i. verkalkten endokarditischen u. endoarterit. Herden, Virchows Arch. f. Anat. **166**:13, 1901.

67. Maximow: Ueber experimentelle Erzeugung v. Knockenmarkgewebe, Anat. Anz. **28**:609, 1906.

and probably also of heteroplastic calcification, will have to be looked for within the cell itself.

Very much has been accomplished toward the final solutions of these various problems by the results of experimentally produced calcification in normal animals as done by Kossa,[68] Wells,[55] Tanaka,[69] Katase [70] and Albrecht.[71] The latter author succeeded in obtaining calcification of heart muscle fibers in rabbits by the injection of influenza bacilli. The information gained by these animal experiments may briefly be summed up thus:

RESULTS

Calcification may be produced in a normal animal by means of introduction of a sufficient amount of calcium salts, which amount is comparatively large.

Calcification may take place practically in any organ, among others, in the heart.

Calcium is excreted mainly by the kidneys, intestines (especially the large intestine) and bronchi.

Calcification may be aided by interference with the calcium excretion and by diminution of the calcium tolerance of the cells of the individual organ.

Degeneration of the tissue diminishes the calcium tolerance of its cells.

The frequency of calcification in the various organs depends on the calcium tolerance of the cells and the physiologic metabolic capacity of the individual organ.

Among the tissue elements which attract calcium salts, the elastic tissue fibers take the first place.

Of interest in this connection also may be the experiments of Werra.[72] He has shown that in animals temporary ligation of the renal artery for one hour may cause calcification of the petechial elements of the kidney. The calcification process is completed within from six to seven days after removal of the ligation. From the eighth day on the calcification begins to be gradually absorbed again, and disappears entirely within from thirty-five to forty-four days, at which time the kidney again presents a normal appearance.

Calcification of the coronary vessels of the heart and of its valves may occur very early in life, as shown by Surbeck,[73] who reports calcification near the aortic valves and of the coronary arteries in an infant, aged 2 days, presenting diplococcus infection with fibrinous pericarditis.

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68. Kossa: Ueber die in Organen kuenstl. erzeugte Verkalkung, Beitr. z. path. Anat. u. z. allg. Path. **29**:163, 1903.

69. Tanaka: Ueber die Kalkresorption und Verkalgungen; Biochem. Ztschr. **35**:113, 1911; **38**:285, 1912.

70. Katase: Experimentelle Verkalkungen am gesunden Tiere, Beitr. z. path. Anat. u. z. allg. Path. **57**:517, 1914; Experimentelle Kalkmetastase, Bern, 1916.

71. Albrecht: Zentralbl. f. allg. Path. u. path. Anat. **20**:1031, 1909.

72. Werra: Ueber d. Folgen d. voruebergehenden u. dauernden Verschlusses d. Nierenarterie; Virchows Arch. f. path. Anat. **88**:197, 1882.

73. Surbeck: Ueber einen Fall v. congenitaler Verkalkung m. vorwiegender Beteiligung d. Aorta, Zentralbl. f. allg. Path. u. path. Anat. **28**:25, 1917.

The investigations by Baeumler [74] show that calcification of arteries is not necessarily a senile condition, but may be produced irrespective of age, by mechanical, toxic, infectious and other influences.

Wells comes to the following conclusions with regard to pathologic calcification: Retrogressive changes are for pathologic calcification, a condition sine qua non, except in metastatic calcification. Deposition of calcium salts in such areas of degeneration depends on: (1) increased alkalinity or decreased carbon dioxid in degenerated tissues causing precipitation of the inorganic salts in the fluids seeping slowly through them; (2) utilization of the protein of the fluids by the starved tissues so completely, because of its slow passage through them, that the calcium cannot be held longer in solution; (3) formation within the degenerated area of a substance or substances having a special affinity for calcium; (4) production of a physiologic condition favoring the local absorption of salts, the least soluble salts accumulating in excess.

SUMMARY

The material just presented shows that there still are many questions to be solved with regard to heteroplastic calcification, within the heart as well as within other parts of the body. We still do not know why it is that, given two cases of exactly the same pathologic conditions, one will present extensive calcification within the heart, while the other one will reveal none. Extensive bone destructive processes are so very frequent, and yet cases of calcium metastasis are so extremely rare. There is hardly any doubt that calcium metastasis or rather "heteroplastic calcium impregnation" really occurs. One may even be justified in stating that it forms a definite clinical entity as described above. The apparently direct taking up by the endocardium of the calcium salts in the auricles, where there are, for obvious reasons, more favorable conditions for such a process to take place than in the ventricles, is even more characteristic of "*metastatic* calcium impregnation" as it really ought to be called, than the coexisting calcification process in the lung, kidneys and stomach.

Some of the discrepancies of opinion, with regard to calcification of the heart, as met with among the authors of the cases enumerated in Table 1, could possibly be explained by the observation that some of them, it seems, have made mistakes such as could occur at similar occasions. In some instances, findings in too small a series of cases have been generalized and quite blindly set down as definite rules for the entire subject of calcification of the heart. In other instances, apparently not quite correct interpretations by the original authors have been

74. Baeumler: Ist die Arteriosclerose eine Allgemeinerkrankung? Berl. klin. Wchnschr. **42**:38, 1905.

indiscriminately accepted as correct by other writers, thus leading to wrong theorizing and incorrect classification, similar to the cases of Heschl and Tilp, and to a certain degree also to that of Wiechert. Furthermore the results gained by experiments in *normal* animals, have been applied, it would seem, occasionally in a somewhat unqualified manner to the human body, where the calcification process very often is the outcome of a combination of *pathologic* conditions in various organs. Especially complicating in this respect is the close interrelationship between cardiac and renal conditions, so that very often it is difficult or even impossible to hold distinctly apart the rôle played by each one of these two factors in the production of myocardial calcification.

Taking into due consideration all the points brought out by the various writers on our subject as briefly mentioned before, and making allowances for apparent slight errors made by some authors of the published cases, one is justified in arriving at the following conclusions.

CONCLUSIONS

Calcification of the heart, like any other pathologic calcification, may occur in two different forms: (1) *deposition* of calcium salts within the cardiac tissue; (2) *precipitation* of calcium salts directly into the endocard.

1. Deposition of calcium salts within the heart takes place only in dead or markedly deteriorated, never in healthy, tissue. The condition is not very uncommon.

The process begins with deposition of fine calcium granules, usually calcium phosphate, within the broken up heart muscle fibers. These calcium granules may gradually coalesce, forming plaques, the latter gradually involving all the elements of the heart substance.

There is no specific clinical cause for the condition, but the calcification can occur in the course of any pathologic condition which gradually leads to degeneration of cardiac muscle fibers of diffuse or localized type.

What rôle pathologic conditions of the kidneys, causing interference with calcium excretion and thereby possibly increase in the total amount of free calcium salts, may play in aiding the production of myocardial or any other pathologic calcification, has not definitely been determined yet.

The ultimate cause of pathologic calcium deposition seems to lie in the factors controlling the calcium tolerance of the cell, and in the character of physicochemical processes within the individual cells.

2. Calcium precipitation involves the endocardium only. It is an extremely rare condition, only two cases being known so far, both of which were observed in combination with the so-called calcium metastasis.

By metastatic calcification is understood the direct deposition or rather precipitation into apparently normal tissue of the overload of circulating calcium salts, produced by extensive bone destructive processes within the body.

The precipitated calcium salts in such cases are found in the kidneys, stomach, lung and occasionally in the auricles of the heart. In the kidneys, the calcification process involves the glomeruli and to a lesser degree also the canaliculi; in the stomach the interstitial tissue of the mucosa, in the lung the elastic tissue, in the heart the endocardium of the left auricle, to a lesser degree also of the right.

Calcium metastasis could be considered a clinical entity, composed of the clinical picture of the primary bone destructive lesion, finally superimposed by a second clinical picture somewhat suggestive of acute rheumatism.

The final causes of calcium metastasis are not definitely known; but it is fair to assume that the main causative factors consist of the oversaturation of the circulation with calcium salts, associated later on with a breakdown of the mechanism normally provided for the excretion of calcium salts, followed finally by precipitation of the calcium overload in the places mentioned in the foregoing.

3. Roentgenologically, calcification of the heart may be demonstrated intra vitam, if extensive enough. In such instances one may even succeed in differentiating it from pericardial calcification.

Small calcified foci within the heart cannot be demonstrated by the roentgen ray during lifetime.

Small, fine, solitary calcified foci within the heart wall may be sometimes overlooked at necropsy. This may be avoided, to a large extent, by taking roentgenograms of the removed necropsy specimen, whereby even very fine calcified areas are clearly demonstrated and localized.

Such necropsy radiographic work, if carried on systematically, will show that myocardial calcification is not so very rare as is generally believed.

The use of the roentgen ray should be considered a very important aid for the pathologist in his search for small calcified foci, and for other changes which cause radiographically sufficient differentiation of tissue densities.

THE RATIONAL USE OF DUODENAL DRAINAGE

AN ATTEMPT TO ESTABLISH A CONSERVATIVE ESTIMATE OF THE VALUE OF THIS PROCEDURE IN THE DIAGNOSIS OF BILIARY TRACT PATHOLOGY *

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Few laboratory methods introduced in recent years have attracted such widespread attention throughout medical circles as the so-called Meltzer-Lyon method of biliary drainage. The literature for the last three years includes at least fifty articles on the subject, and the method has been widely used throughout this country, as well as in England and on the Continent. A review of the literature would be of little value, as many of the articles are merely clinical impressions, and are not based on careful investigative work. It may be said, however, that the various articles fall roughly into two groups, those upholding, and those denying the value of duodenal drainage. According to Lyon,[1] Smithies, Karshner and Oleson,[2] White,[3] and others, the method is of great value in the diagnosis and treatment of practically all kinds of biliary tract pathologic changes. Einhorn,[4] Alvarez,[5] Cutler and Newton,[6] and others, on the other hand, believe that the method is of little or no real value. The conclusions of each of these groups are largely based on rather indifferently controlled clinical studies. In addition, there is a third group of men who have confined their comment largely to the results of animal experimentation. The work of this group

* From the Medical Service of the Massachusetts General Hospital. (This paper is No. 15 of a series of studies in metabolism from the Harvard Medical School and allied hospitals, the expenses of which have been defrayed in part by a grant from the Proctor Fund of the Harvard Medical School for the Study of Chronic Diseases.)

1. Lyon, B. B. V.: Diagnosis and Treatment of Diseases of the Gallbladder and Biliary Ducts, J. A. M. A. **73**:980 (Sept. 27) 1919.

2. Smithies, F.; Karshner, C. F., and Oleson, R. B.: Nonsurgical Drainage of the Biliary Tract, J. A. M. A. **77**:2036 (Dec. 24) 1921.

3. White, F. W.: The Value of Medical Biliary Drainage in Diagnosis and Treatment of Diseases of the Gallbladder and Bile Ducts, Boston M. & S. J. **186**:206 (Feb. 16) 1922.

4. Einhorn, M.: Action of Various Salts and Other Substances on the Liver After Their Introduction into the Duodenum, New York M. J. **114**:262 (Sept. 7) 1921.

5. Alvarez, W. C.: Diagnosis and Treatment of Gallbladder Disease with Special Reference to the Meltzer-Lyon Test, M. Clin. N. Amer. **6**:213 (Sept.) 1922.

6. Cutler, E. C., and Newton, F. C.: Some Experiences with the "Meltzer-Lyon" Test in Gallbladder Disease, Surg., Gynec. & Obst. **35**:146 (Aug.) 1922.

includes papers by Auster and Crohn,[7] Friedenwald, Martindale and Kearney,[8] Frazer,[9] Diamond,[10] McWhorter,[11] and a few other authors. A careful survey of the literature seems to indicate that as yet a conservative and fair estimate of the value of duodenal drainage has not been made.

Unquestionably, the early, rather extravagant claims for the method, as a means of diagnosis and treatment, have not been fulfilled. It is also unfortunately true that much of the criticism and pessimism with which the subject is now viewed is due to the claims that have been made by some enthusiasts as regards the efficacy of treatment by duodenal drainage. The undoubted psychologic effect produced by such treatment has undoubtedly been overlooked, or not mentioned by many. On the other hand, the somewhat unequivocal stand of Alvarez [5] and other authors, that the method is without any value, seems equally unjustifiable. It is the purpose of this paper to present evidence that duodenal drainage is justifiable in a selected group of cases, and that in this group it is of definite diagnostic or therapeutic value.

Before discussing the therapeutic value of duodenal drainage, I wish to comment briefly on the experimental evidence at hand that bears on the physiology of the gallbladder and the sphincter of Oddi. According to the early experiments of Doyon,[12] Bainbridge and Dale,[13] Freese,[14] and Okada,[15] the gallbladder is capable of producing muscular contractions, the frequency and intensity of which may be modified by various stimuli. The introduction into the duodenum, for instance, of acid chyme, increases the strength and frequency of such contractions. Other stimuli, such as morphin, were observed to produce an opposite result.

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7. Auster, L. S., and Crohn, B. B.: Notes on Study of the Physiology of the Gallbladder, Am. J. M. Sc. **164**:345 (Sept.) 1922.

8. Friedenwald, I.; Martindale, J. W., and Kearney, F. X.: Animal Experiments on Certain Phases of the Lyon-Meltzer Method of Biliary Drainage, J. Metab. Res. **2**:349 (Sept.) 1922.

9. Frazer, E. B.: The Effect of Magnesium Sulphate on the Secretion of Bile, J. A. M. A. **79**:1594 (Nov. 4) 1922.

10. Diamond, J. S.: An Experimental Study of the Meltzer-Lyon Test, with Comment on the Physiology of the Gallbladder and Sphincter Vateri, Am. J. M. Sc. **166**:894 (Dec.) 1923.

11. WcWhorter, G. L.: The Surgical Significance of the Common Bile Duct Sphincter, Surg., Gynec. & Obst. **32**:124 (Feb.) 1921.

12. Doyon, M.: Contribution a l'étude de la contractilité des voies biliares, Arch. de Physiol. norm. et path. **25**:678, 1893.

13. Bainbridge, F. A., and Dale, H. H.: The Contractile Mechanism of the Gallbladder and Its Extrinsic Nervous Control, J. Physiol. **33**:138, 1905 and 1906.

14. Freese, J. A.: The Force of Contraction of the Gallbladder and the Course of Its Motor and Inhibitory Nerve Fibers, Bull. Johns Hopkins Hosp. **16**:235, 1905.

15. Okada, S.: Contractile Movements of the Gallbladder, J. Physiol. **50**:42, 1915.

The exact mechanism controlling the activity of the gallbladder has been proved to depend on two sets of nerve fibers, one motor, and the other inhibitory. Later Meltzer [16] conceived the idea of a coordinated nervous control of the sphincter of Oddi and the gallbladder musculature, of such a nature that stimuli causing a relaxation of the sphincter simultaneously caused a contraction of the gallbladder, and vice versa. Although never proved experimentally, this idea of a contrary innervation in the biliary system was rather generally accepted, and at present forms the basis of the so-called Meltzer-Lyon method of nonsurgical biliary drainage. The method was based on a theoretical suggestion made by Meltzer that the instillation of a solution of magnesium sulphate into the duodenum would cause a relaxation of the sphincter of the common bile duct, and a simultaneous contraction of the gallbladder. Such a theory, if true, would quite logically afford a rational means of studying and treating gallbladder pathology, and the widespread acceptance of Lyon's original work is testimony to the apparent rationality of the hypothesis. Recent experimental work, however, points against the soundness of Meltzer's, and subsequently Lyon's, theory of "contrary innervation," and to a rather large degree invalidates Lyon's claims and methods. A review of Bainbridge and Dale's, and Okada's original work indicates that, while gallbladder contraction can be demonstrated, such contractions were so slight as to require very delicate and highly magnified methods to show clearly their existence. Furthermore, it must be recalled that a large majority of the gallbladders investigated by Lyon's technic are diseased organs, with thickened and fibrosed walls. It appears inconceivable that a chemical stimulus applied to the duodenal mucosa can produce contractions in gallbladders, diseased or otherwise, of sufficient magnitude to empty the organ. The work of Auster and Crohn [7] on animals suggests that the action of magnesium sulphate, when introduced into the duodenum, does not cause a contraction of the gallbladder. Clinical observations, following the use of intraduodenal magnesium sulphate during laparotomy, have given conflicting results. The majority of observers agree that under such conditions no contraction or emptying of the gallbladder occurs. All such evidence is, however, open to the criticism that normal nerve reactions were abolished by the anesthesia, and is therefore of little value. That magnesium sulphate does relax the duodenum in the majority of instances, when introduced therein, is definitely proved by the work of Frazer [9] on animals. This investigator produced evidence

16. Meltzer, S. J.: The Disturbance of the Law of Contrary Innervation as a Pathogenic Factor in the Diseases of the Bile Ducts and the Gallbladder, Am. J. M. Sc. **153**:469 (April) 1917.

that the action of the drug is purely local, Einhorn,[4] Dunn [17] and others to the contrary notwithstanding. Similar experimental results were obtained by Friedenwald, Martindale and Kearney [8] on dogs. These workers not only obtained no evidence of central action following the use of the drug, but were also unable to demonstrate any contraction of the gallbladder. Recent work by Diamond [10] appears, at last, to produce unanswerable proof of the inaccuracy of Lyon's original hypotheses. In Diamond's experiments on dogs with duodenal fistula, repeated intraduodenal injections of a solution of magnesium sulphate, in ambulatory animals, failed to show expulsion into the duodenum of carmin previously introduced into the gallbladder. These experiments covered a reasonable period of time (from six to eight days), and during the entire period no macroscopic evidence of carmin appearing in the duodenum could be obtained. Occasionally, rare microscopic particles of the dye were seen, but no evidence of gross gallbladder contractions could be elicited. In the presence of such carefully controlled experiments, and especially in view of the notable absence of any experimental work in favor of Lyon's theories, it would seem illogical to accept longer the hypothesis that there exists a crossed innervation between the sphincter of Oddi and the gallbladder musculature, or that magnesium sulphate, peptones, hydrochloric acid, or other substances, when introduced into the duodenum, do more than cause a local relaxation of the duodenal wall, and with it the muscle fibers of the sphincter of Oddi.

With regard to the value of the sequence of "A," "B" and "C" biles, the before mentioned evidence would destroy the possibility of real significance attaching to color changes in the bile flowing into the duodenum. Surely, if gallbladder contractions are not to be expected following magnesium sulphate lavage, so-called "B" bile loses its significance. Clinically, it has been shown that "B" bile can be observed, even in cases of obstructed cystic duct, or in the absence of the gallbladder.[17] I have frequently observed such a phenomenon, and have proved the presence of increased bile pigments by spectroscopic analysis. Consideration of the cases in which "B" bile has been noted, in the absence of the gallbladder, indicates that in these cases there was an associated involvement of the entire biliary tract, with resulting liver disturbance. In a previous article [15] I have already shown that under such conditions of hepatic disturbance the liver bile is practically always very dark, due to increased pigment content. What, then, is the logical explanation of the so-called "gallbladder" or "B" fraction? A reasonable explanation

17. Dunn, A. D., and Connell, K.: Report of a Case of Hepatoduodenostomy, J. A. M. A. **77**:1093 (Oct.) 1921.

18. Jones, C. M.: Blood Pigment Metabolism and Its Relation to Liver Function, Arch. Int. Med. **29**:643 (May) 1922.

would seem to be that the fraction of duodenal contents containing the highest concentration of bile pigments is merely that portion collected during the greatest flow of bile into the duodenum, i. e., during the greatest relaxation of the sphincter of Oddi, following the use of magnesium sulphate. As soon as the relaxation of the duodenum and sphincter diminishes, the flow of bile also diminishes and the amount of bile pigment per unit volume of duodenal contents is correspondingly lowered. Subsequent fractions are, therefore, lighter in color, although repeated instillations of magnesium sulphate will produce continued increases in pigment. Such an explanation is simple, it does not depend on unproven hypotheses, and incidentally deprives the method of much of its picturesque appeal. That the duodenal contents may contain small amounts of gallbladder bile, however, is probable, and is suggested by the finding of microscopic amounts of carmin in Diamond's experiments, which have already been alluded to. Such small amounts of gallbladder bile can undoubtedly be accounted for by passive siphonage during an increased flow of liver bile.

From experimental and clinical evidence, therefore, it seems justifiable to conclude that the diagnosis and treatment of gallbladder pathologic changes, based on the collection "gallbladder" bile, is extremely illogical and unwarranted. Of what use, then, is duodenal lavage, either in the diagnosis or treatment of biliary tract pathologic changes? In spite of the before mentioned adverse criticism, which I think is warranted, I believe that the method can be intelligently used in selected cases to distinct advantage, both therapeutically and as a diagnostic measure.

Attempts to treat chronic disease of the gallbladder by duodenal lavage with instillations of magnesium sulphate, or other solutions, seem to be illogical for reasons before mentioned. Gallbladder drainage by such means must be, at most, microscopic in amount. In addition, it is well to recall that the pathologic changes of chronic cholecystitis lies in the walls of the organ, and not in the mucosa or in the bile contained in the viscus. With such a pathologic picture the hope of curing such a process by ineffective gallbladder "drainage" appears remote. In cases of acute cholecystitis, in which the organ is presumably under increased tension, prolonged complete relaxation of the sphincter of the common bile duct, with a resulting free flow of bile, may conceivably aid in a passive partial evacuation of the gallbladder with slight relief of symptoms. Cholelithiasis need only be mentioned as a condition not amenable to any forms of medical therapy, except for symptomatic relief. The psychologic element of bile drainage must be emphasized, and undoubtedly accounts for many "cures" of "chronic cholecystitis"—a disease at best presenting an extremely difficult diagnostic problem.

A similar criticism might be justified, in passing, of the relief following duodenal drainage, claimed in such diseases as diabetes mellitus, hemolytic jaundice, etc.

One type of disease of the biliary tract can be successfully treated by this method. Sufficient clinical evidence has been presented to warrant the conclusion that infectious (catarrhal) jaundice can be relieved, and the course of the disease shortened by frequent duodenal lavage. The procedure is logical in such cases, inasmuch as the local effect of the magnesium sulphate solution allows a relaxation of the sphincter of Oddi, with a resulting flow of bile. As the pathologic changes of infectious jaundice lies primarily in the liver, biliary drainage offers a feasible method of treatment. Observations by Lyon [19] and others have already indicated the value of such treatment, and a recent communication by Jones and Minot [20] shows graphically the probable results of duodenal drainage in cases of infectious jaundice. It seems probable, by analogy, that a similar procedure in cases of arsphenamin jaundice is warranted. Observations on several cases indicate that favorable results may be expected.

From the nature of the pathologic changes of other diseases of the biliary system, duodenal drainage in cirrhosis, cancer, etc., would hardly be expected to be a rational form of therapy.

From the point of view of exact diagnosis, the value of duodenal analysis is also limited. A study of the bacteriology of the duodenal contents is now generally considered to be of little value. Contamination cannot be excluded, even by the most rigid technic, and positive cultures, even when obtained, rarely give an indication of the location or of the type of the existing pathologic changes. One exception must be made to this rather general statement. The detection of typhoid carriers can readily be made by culture of the duodenal contents, but no special precautions have been found necessary, in my experience, beyond a sterile duodenal tube.

For diagnostic purposes there remains, then, the examination of the duodenal contents for (1) bile pigments, (2) cellular elements and (3) crystalline elements.

Although the attempts to divide the duodenal contents into "A," "B" and "C" fractions are of little or no value, for reasons already given, estimations of the amounts and types of bile pigments present in a given specimen are of some importance. It has been shown by numerous observers that the concentration of the bile pigments is abnormally high

19. Lyon, B. B. V.: The Treatment of Catarrhal Jaundice by a Rational Direct and Effective Method, Am. J. M. Sc. **159**:503 (April) 1920.

20. Jones, C. M., and Minot, G. R.: Infectious (Catarrhal) Jaundice; an Attempt to Establish a Clinical Entity, Boston M. & S. J. **189**:531 (Oct. 18) 1923.

in cases associated with increased blood destruction. The writer has confirmed these findings, and in addition, has shown that an increase of the bile pigments in the duodenal contents occurs in various types of liver disturbance.[18] Inspection of the results obtained in approximately 600 analyses has shown that the pigment content of the bile is increased in (1) pernicious anemia, hemolytic jaundice, malaria, hemolytic streptococcus septicemias, Banti's disease, paroxysmal hemoglobinuria, certain cases of polycythemia, acute lead poisoning, and (2) in certain phases of infectious (catarrhal) jaundice, diarsenol jaundice, some of the cirrhoses, cancer of the liver, and many cases of chronic cholecystitis and cholelithiasis, chronic passive congestion of the liver, and other types of liver disturbance, including the majority of cases of diabetes mellitus. The high bile pigment concentration observed in cases of chronic cholecystitis and cholelithiasis I believe to be due, not to stasis of bile in the gallbladder, but probably to an associated disturbance of the liver, a common occurrence in chronic gallbladder disease. Examination has also shown that in cases associated with abnormal blood destruction, or with alteration of liver function, not only are the total bile pigments increased in amount in the duodenal contents, but the presence of abnormal proportions of the various pigments also occurs. Normally, the bile contains bilirubin and urobilin and occasionally small traces of urobilinogen. In abnormal blood destruction, and in cases of marked liver disturbance, the proportion of urobilin or urobilinogen increases strikingly, and rarely one finds the rare pigment cholecyanin. A detailed discussion on the significance of changes in the bile pigments is to be found in articles already published.[21] Briefly, then, an abnormal pigment content of the bile may indicate the existence of one of several disease conditions, but is not conclusive evidence of the presence of any single disease.

Turbidity and increased viscosity of the duodenal contents have been frequently mentioned as of diagnostic significance. They may be due to many causes besides biliary tract pathologic changes, and may be entirely wanting in the presence of marked biliary disease. They are of no diagnostic importance.

Microscopic examination alone seems to be of practical value in the diagnosis of biliary disease by means of duodenal drainage. Such a statement is partly in harmony with Lyon's original claims, but is distinctly contrary to the conclusions of numerous investigators, including Alvarez,[5] Cutler and Newton[6] and others. In my experience, a careful examination of a large number of sediments of duodenal contents has shown that certain features may be of diagnostic significance.

21. Jones, C. M.: Alterations in Liver Function and in the External Secretory Activity of the Pancreas in Diabetes Mellitus: A Preliminary Report, Boston M. & S. J. **189**:851 (Nov. 29) 1923; also Footnotes 18 and 20.

Bile-stained leukocytes and epithelial cells in any quantity are not found in normal patients. They do occur in the presence of an inflammatory condition involving the biliary tract, although it is not possible to determine from the type of cell found in the duodenal sediment the exact level of the inflammatory process. In infectious (catarrhal) jaundice there is a large amount of such bile-stained cellular material during the early stages of the disease. In acute cholecystitis similar findings may be obtained, but are not constant, and other clinical and laboratory findings are of much greater diagnostic value. The exact information to be derived from a study of the cellular elements of the duodenal contents may be said, therefore, to be largely confirmatory. Too much reliance cannot be placed on the mere finding of abnormal amounts of bile-stained cells, although in most cases such findings indicate biliary tract inflammation. The significance of such findings will receive further comment.

There remains but to mention the finding of abnormal crystalline elements in the duodenal contents. In my experience, based on the analysis of a large number of cases, the finding of abnormal amounts of cholesterin, bilirubin or calcium bilirubinate has been of real diagnostic value. As already indicated, the attempted segregation of different samples of bile and the localization therefrom of biliary pathologic changes, by attention to color, bacteriology, or cellular elements, has not proved logical or susceptible of proof. On the other hand, careful examination of the following results would seem to indicate that the finding of abnormal crystalline elements in the duodenal contents is of diagnostic significance, and in itself warrants the use of a time consuming and unpleasant laboratory method.

CLINICAL MATERIAL

The clinical material forming the basis of this investigation consists of three groups of cases, with a total of 274 individual patients. The first group, the findings in which are shown in Table 1, consists of fifteen normal controls. The members of the group were normal medical students and members of the laboratory staff. The second group is comprised of 202 patients, taken from the medical and surgical wards of the Massachusetts General Hospital. As shown in Table 2, the patients included in this group were suffering from various types of disease; in all, twenty-seven different diseases were diagnosed. This group, therefore, may be considered as a group of pathologic controls. The third group of cases (Tables 3, 4 and 5) was made up of fifty-seven patients with a definite diagnosis of cholelithiasis. Of the fifty-seven patients in this series, forty-two were operated on and were proved to have had gallstones. The remaining fifteen cases were patients in which the diagnosis was perfectly obvious, and was agreed on by both medical

and surgical consultants. Operation was not performed on these patients because of their general condition, or because of their unwillingness to undergo laparotomy.

METHOD

The following description of the method employed in collecting and examining the duodenal contents will be seen to differ in certain essential details from that described by Lyon and others. Following the introduction of the duodenal tube into the duodenum, the position of the tip was carefully checked by fluoroscope. Other means of determining the exact position of the tube have been found to be inaccurate, and often misleading. An instillation of 60 c.c. of warm 33 per cent. magnesium sulphate solution was then made into the duodenum, and immediately thereafter passive siphonage was begun. No suction apparatus was employed. As soon as a flow of bile was established, the duodenal contents were collected in brown glass bottles, and siphonage continued for one-half hour. The tube was then withdrawn, and the duodenal contents well mixed and centrifuged at once at high speed for fifteen minutes. This high speed centrifugalization is extremely important, and failure to obtain a sediment in this manner accounts for many of the failures to get consistent and satisfactory results (examination of specimens "fished" out of the duodenal contents cannot be expected to yield consistent results). The sediment obtained by high speed centrifuging was carefully drawn from the centrifuge tubes, after decanting the supernatant fluid, and examined microscopically. Note was made of clumps of cholesterin crystals, bilirubin or calcium bilirubin, and abnormal amounts of bile-stained cellular elements. At the same time, a portion of the duodenal contents was examined spectroscopically for the concentration and types of bile pigments. Although probably not of any absolute diagnostic significance, the bile pigment estimations, made during the course of this investigation, are included in the accompanying tables to indicate the type of pigment findings in the different diseases studied. The method of pigment estimation has been frequently described, and is briefly as follows:

To 10 c.c. of duodenal contents add an equal amount of a saturated alcoholic solution of zinc acetate. This is shaken and filtered, and to 10 c.c. of the filtrate is added 1 c.c. of Erlich's reagent. This solution is allowed to stand in the dark for fifteen minutes, and is then examined spectroscopically for the presence of bilirubin, urobilin and urobilinogen. The number of dilutions with 95 per cent. alcohol necessary to remove the characteristic absorption band of a given pigment is taken as the relative amount of that pigment in a given specimen. The absorption bands of urobilin and urobilinogen are absolutely characteristic. Although it is said that bilirubin gives no characteristic shadow in the spectrum, I have found that pure solutions of this pigment give a distinct characteristic shadow in the blue-violet end of the spectrum. As the concentration of this pigment increases, the shadow involves the blue-green, and even the yellow-green. In such instances the shadow includes the band made by the urobilin present, and renders it impossible to estimate the latter pigment.

In this even the original sample, after being treated with zinc acetate and Erlich's reagent, is split in two portions. One specimen is examined for the presence of bilirubin and urobilinogen, and the dilutions estimated. The second fraction is treated with an equal amount of a 10 per cent. solution of calcium chlorid. The addition of the calcium precipitates sufficient bilirubin to permit the estimation of the urobilin present. In normal persons the normal pigment concentrations have been found to be: bilirubin, from 60 to 150 dilutions; urobilin, from 4 to 12 dilutions; urobilinogen, from 0 to 4 dilutions. At the time this investigation was commenced, attempts to estimate the urobilin content were unsatisfactory, and, as a result, many of the cases included in the tables have no figure for urobilin.

LABORATORY DATA

The results of the findings made in the various cases studied during the course of this investigation are given in tabulated form.

NORMAL CONTROLS

Table 1 needs no explanation. The normal controls (fifteen) all showed negative sediments and normal bile pigment concentration in the duodenal contents.

TABLE 1.—*Duodenal Findings in Normal Controls*

Number of Cases	History	Physical Examination	Bile Pigments	Sediment
15	Negative	Negative	Average, 87 dilutions	Negative

FINDINGS IN TWO HUNDRED AND TWO PATHOLOGIC CONTROLS

The findings made in the group of pathologic controls (Table 2) require comment. Of the 202 cases of patients with twenty-seven different diseases, 126, or approximately 62 per cent., showed negative sediments. The remaining 38 per cent., or seventy-six patients, showed some abnormality of duodenal sediment either cellular or crystalline in nature. It is to be noted, however, that in eighteen instances these abnormalities consisted only of very rare cellular or crystalline elements. Of the seventy-six cases with abnormal sediments, sixty-seven were in patients with definite or probable biliary tract pathology, and were so noted in the table. Seven had diabetes mellitus and probable cholelithiasis. Twenty-three had infectious (catarrhal) jaundice, and showed the findings elsewhere described as characteristic of that disease. The remaining ten patients with this disease were examined at a period when abnormal sediment findings were not to be expected. Nine patients with abnormal sediments had chronic cholecystitis, although twelve others with this disease showed no abnormality. Out of twenty-two patients with liver disease, fifteen showed abnormal sediments. Two out of six patients with cancer of the pancreas showed abnormalities, and these two patients were jaundiced, and showed definite involve-

ment of the biliary system. Two patients with portal thrombosis, one patient with typhoid fever with right upper quadrant pain and tenderness, one patient with duodenal ulcer and gallbladder adhesions (proved at operation), and one patient with chronic biliary tract disease with

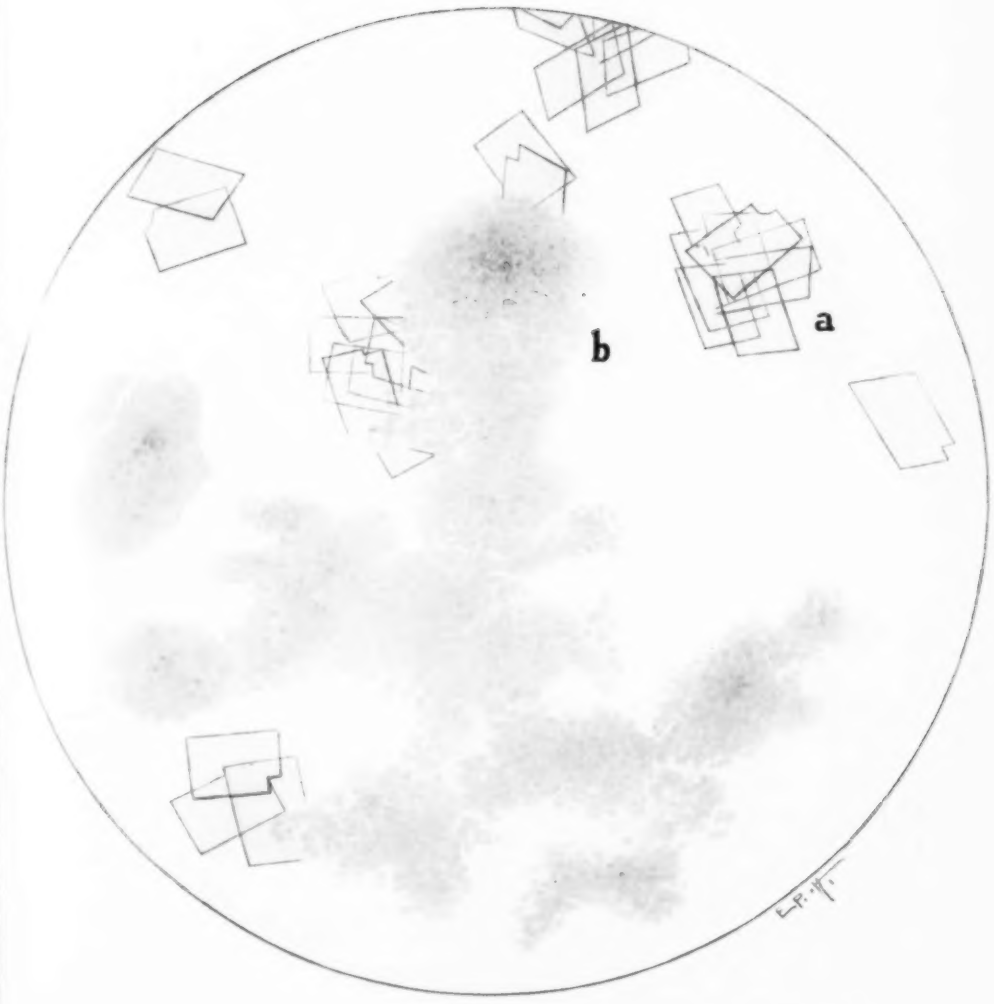
TABLE 2.—*Findings in Two Hundred and Two Pathologic Controls*

		Sediment Findings					
Clinical Diagnosis	No. Cases	Negative	Abnormal	Bile-stained Cells	Cholesterin Crystals	Bile Pigment Crystals	High Bile Pigments
Diabetes mellitus (7* cases with probable gallstones)	63	52	11	7*	5	6	51
Infectious (catarrhal) jaundice*	33	10	23	13	2 (rare)	11	16
Chronic cholecystitis*	21	12	9	6	1	8 (4 rare)	7
Cirrhosis of liver (syphilitic)*	2	0	2	0	0	2	0
Cirrhosis of liver (alcoholic)*	3	3	0	0	0	0	1
Cirrhosis of liver (infectious)*	5	1	4	4	1 (rare)	0	1
Chronic hepatitis*	8	1	7	4	3 (rare)	4 (2 rare)	1
Carcinoma of liver*	3	2	1	0	0	1	2
Portal thrombosis*	2	0	2	2	2	2	2
Banti's disease*	1	0	1	1	1 (rare)	0	1
Cancer of pancreas (5* cases with jaundice)	6	4	2	2	0	1	1
Acute pancreatitis †	1	0	1	0	0	1	1
Hemolytic jaundice †	2	0	2	2	0	2	2
Pernicious anemia †	9	6	3	0	2 (rare)	1	5
Typhoid (1* with right upper quadrant pain)	3	2	1	0	1	0	0
Visceroptosis and neurosis	10	8	2	1 (rare)	0	1 (rare)	1
Peptic ulcer (1* case with gallbladder adhesions)	9	7	2	1	0	2 (rare)	0
Chronic appendicitis	1	0	1	1	0	0	0
Ruptured appendix	1	1	0	0	0	0	0
Lead poisoning	3	3	0	0	0	0	1
Hemochromatosis	3	3	0	0	0	0	0
Chronic arthritis	2	2	0	0	0	0	0
Postoperative adhesions (1* old gallbladder operation)	3	2	1*	1	0	0	0
Chronic purpura hemorrhagica	2	2	0	0	0	0	1
Polycethemia vera	1	1	0	0	0	0	0
Arteriosclerosis	1	1	0	0	0	0	0
Malaria	1	1	0	0	0	0	1
Bilharziasis ‡	1	1	0	0	0	0	0
No pathology at operation	2	1	1	1	1	1	0
	202	126	76	46	19	43	96

	Number	Per Cent.
1. Total number abnormal sediments in 202 cases	76	37.5
2. Total number cases with abnormal sediments and undoubted biliary tract pathology	67	33.3
3. Total number cases with marked abnormalities of sediment	58	28.7
4. Total number cases with rare abnormalities of sediment	18	9.0
5. Total number cases with unexplained abnormality of sediment	9	4.5
4. Total number cases with rare abnormalitis of sediment	18	9.0
7. Total number cases with abnormal cholesterin sediment and no biliary tract pathology proven	1	0.5

* Cases with undoubted liver or gallbladder pathology.
† Cases with probable functional disturbance of liver or bile tract.
‡ Bilharzia eggs found in duodenal sediment.

previous cholecystectomy and postoperative adhesions (found at the second operation), all showed abnormal duodenal sediments. Of the six remaining patients with probable biliary tract involvement, three had pernicious anemia, two had hemolytic jaundice, and one had acute hemorrhagic pancreatitis (examined following operation). Pernicious



Typical duodenal sediment in cholelithiasis. *a*, cholesterin crystals; *b*, bile pigment crystals.

anemia is well known for the abnormal character of bile associated with the disease, and it is not surprising to have found evidences of occasional precipitated crystalline elements in these cases. Cases of hemolytic jaundice always show an abnormally high concentration of the bile pigments in the duodenal contents, and it is known that about two-thirds of all patients with this disease have pigment stones in the gallbladder or bile ducts. The findings in the two patients examined were, therefore, to be expected. Acute hemorrhagic pancreatitis, because of its close anatomic relation to the biliary tract, might well be expected to involve at least the larger bile ducts.

Thus, out of seventy-six patients showing abnormal duodenal sediments, sixty-seven can be shown to have had involvement of some portion of the biliary system. It is to be observed that of these sixty-seven abnormal sediments, forty-three showed abnormal amounts of bile-stained epithelium and leukocytes, forty showed abnormal amounts of precipitated bile pigment crystals, and only eighteen showed cholesterin crystals. Of the forty patients showing abnormal amounts of bile pigment crystals, seven showed only "rare" traces, which probably had best be disregarded. Of the remaining thirty-three patients, six were presumably cases of cholelithiasis, and twenty-four of the patients showed marked liver involvement.

Of the eighteen patients showing cholesterin crystals in the duodenal sediment, nine showed only very rare crystals, and may also be disregarded. Of the remaining nine patients, five were probable cases of cholelithiasis, two were probable cases of cholecystitis, and two were cases of portal thrombosis. One patient at operation showed no demonstrable pathologic changes.

Of the forty-six patients showing abnormal amounts of bile-stained cells, forty-three showed biliary tract involvement.

Of the 202 patients, therefore, only seventy-six showed any abnormality of sediment, and of these, only nine could not be accounted for on the basis of biliary tract pathologic change. Thus, less than 5 per cent. of the cases in this group presented unexplained sediment abnormalities.

It would seem logical, therefore, to assume that duodenal sediments containing abnormal amounts of bile-stained cells, bile pigment crystals, or cholesterin crystals, usually are associated with biliary tract pathologic changes. It is equally logical to conclude, however, that such findings do not in themselves give any indication of the exact locus of such pathologic changes. Abnormal sediments were found in this group in at least seventeen different conditions, and were not characteristic of any single disease entity with the exception of the findings made on patients with diabetes mellitus and probable coexisting cholelithiasis.

Several incidental findings made during the study of this group of patients are of interest. In three patients, *Lamblia intestinalis* were observed in the duodenal contents. Similar findings have been reported by others, and in these patients the finding of these parasites was of no clinical importance. One of the three typhoid patients had the original infection many years prior to examination and was being studied as a carrier. Although no unusual precautions were used, except using a sterile duodenal tube and sterile culture tubes, there was no difficulty in obtaining positive cultures of typhoid bacilli. A second typhoid carrier was similarly proved in one of the patients with cholelithiasis included in Table 4. This second patient came to operation, and, following cholecystectomy, failed to show typhoid bacilli on subsequent examinations. The findings in the patient with bilharziasis are of rather

TABLE 3.—*Findings in Fifty-Seven Cases of Cholelithiasis*

	Unoperated Cases		Operated Cases	
	Number	Per Cent.	Number	Per Cent.
Number of cases	15	....	42	....
Abnormal sediment	15	100.0	42	100.0
Cholesterin	1	6.7	3	7.2
Bilirubin	8 (15)	53.3	24 (41)	57.0
Cholesterin and bilirubin	6	40.0	14	33.0
Bile-stained cells	5	33.3	16	38.0
Abnormal bile pigments	8	53.3	21	50.0
History typical for gallstones	15	100.0	28	66.6
History questionable for gallstones	0	0.0	5	12.0
History misleading for gallstones	0	0.0	6	14.3
History negative for gallstones	0	0.0	3	7.1
Physical examination positive	11	73.3	21	50.0
Physical examination questionable	3	20.0	10	24.0
Physical examination misleading	0	0.0	2	4.7
Physical examination negative	1	6.7	9	21.4
Roentgen ray taken	13	86.6	34	81.0
Roentgen ray positive for gallstones	1	6.6	2	4.7
Roentgen ray suggests gallbladder pathology	6	40.0	13	31.0
Roentgen ray negative	6	40.0	19	45.0

unusual interest. This patient was examined on several occasions, and *Schistosoma hematobium* eggs were easily found in the duodenal contents as well as in the urine. They subsequently disappeared after an extensive course of treatment. I believe this patient is the only case on record in which schistosoma eggs have been found in the duodenal contents.

FINDINGS IN FIFTY-SEVEN CASES OF CHOLELITHIASIS

In rather definite contrast to the above findings are the results obtained in studying fifty-seven cases of cholelithiasis. These cases were not selected, but were taken indiscriminately from the medical and surgical wards of the hospital. A number of the patients had histories of physical findings that were atypical of gallstones, or else were absolutely misleading. Such patients were examined at the request of the medical or surgical service involved. For the sake of convenience

the patients are tabulated in two groups: (1) those patients coming to operation, and (2) those not operated on. Forty-two patients were operated on, and showed gallstones either in the gallbladder or bile

TABLE 4.—*Findings in Operated Gallstone Cases Examined*

						Duodenal Sediment			Pigments			
Case	Sex*	Age	History	Physical Examination	Roentgen Ray	Cholesterin	Bilirubin	Bile-stained Cells	Urobilinogen	Urobilin	Bilirubin	Operative Findings
1	♀	47	Pos.	Pos.	Neg.	+	+	+	8	—	50	Gallstones
2	♀	44	Pos.	Neg.	Neg.	..	+	..	0	—	24	Gallstones
3	♀	49	Pos.	Ques.	Neg.	..	++	..	0	—	80	Gallstones
4	♀	40	Pos.	Neg.	Neg.	..	++	..	0	—	90	Gallstones
5	♀	37	Ques.	Neg.	Ques.	+	++	..	6	—	24	Gallstones
6	♂	47	Pos.	Pos.	Pos.	..	++	+	0	—	21	Gallstones and diabetes
7	♂	45	Pos.	Ques.	Ques.	..	++	+	5	—	100	Gallstones
8	♀	52	Pos.	Ques.	Neg.	..	+	..	0	—	25	Gallstones
9	♀	25	Pos.	Pos.	Ques.	..	++	..	5	—	30	Gallstones; no gallbladder
10	♀	35	Neg.	Neg.	Not done	..	++	..	0	—	250	Gallstones; typhoid carrier
11	♀	19	Misl.	Misl.	Neg.	..	+	++	—	—	—	Gallstones
12	♂	39	Pos.	Pos.	Ques	++	++	..	0	—	80	Gallstones
13	♀	35	Pos.	Pos.	Ques.	+	..	+	0	—	65	Gallstones
14	♀	42	Pos.	Pos.	Neg.	+	++	..	0	—	200	Gallstones
15	♀	48	Misl.	Ques.	Neg.	+++	+++	..	0	—	200	Gallstones
16	♀	12	Pos.	Pos.	Not done	..	++++	..	0	—	315	Gallstones; hemolytic jaundice
17	♀	64	Pos.	Pos.	Ques.	..	+	+	0	—	117	Gallstones
18	♀	49	Ques.	Ques.	Not done	..	++++	..	48	—	98	Gallstones; diabetes
19	♀	50	Pos.	Pos.	Not done	..	+++	..		High		Gallstones; diabetes
20	♀	64	Pos.	Pos.	Neg.	++	++	..	0	—	127	Gallstones
21	♀	17	Pos.	Ques.	Neg.	..	+	+		Very high		Gallstones
22	♂	47	Pos.	Neg.	Ques.	..	++	+	8	—	108	Gallstones
23	♀	73	Pos.	Pos.	Neg.	..	++	..		Very low		Gallstones
24	♀	60	Neg.	Ques.	Not done	++	++	..	20	—	108	Gallstones in cystic duct
25	♂	42	Pos.	Pos.	Neg.	..	++	+	0	—	28	Gallstones
26	♂	55	Pos.	Neg.	Ques.	+	+++	..	6	—	172	Gallstones
27	♂	40	Misl.	Neg.	Neg.	+	+	+	0	—	60	Gallstones
28	♂	58	Pos.	Misl.	Not done	++	+++	..	2	0	300	Gallstones
29	♀	56	Ques.	Neg.	Pos.	+++	++	..	4	22	388	Gallstones; diabetes
30	♀	43	Pos.	Pos.	Neg	+	++	..	0	—	21	Gallstones
31	♀	45	Pos.	Pos.	Not done	..	+++	..	0	—	197	Gallstones
32	♂	24	Misl.	Ques.	Ques.	+++	..	..	0	4	180	Gallstones
33	♀	33	Misl.	Neg.	Neg.	+	+++	..	0	12	200	Gallstones; visceroptosis
34	♀	48	Ques.	Pos.	Neg.	..	++	++	4	22	108	Gallstones
35	♀	40	Pos.	Pos.	Neg.	++	..	..	22	40	108	Gallstones
36	♀	58	Pos.	Pos.	Neg.	..	+	+	0	12	48	Gallstones
37	♀	52	Ques.	Pos.	Not done	++++	++++	..	5	12	120	Gallstones
38	♂	65	Pos.	Pos.	Ques.	..	+++	+	0	4	50	Gallstones
39	♂	45	Misl.	Ques.	Neg.	..	+	++	0	—	40	Gallstones
40	♀	42	Pos.	Pos.	Neg.	..	++	+	4	—	22	Gallstones
41	♀	30	Pos.	Pos.	Ques.	..	(rare)	++	30	20	100	Gallstones
42	♂	60	Neg.	Ques.	Ques.	..	++	+	0	4	80	Gallstones; cirrhosis of liver

Pos., positive; Neg., negative; Ques., questionable; —, not done; Misl., misleading; +, present in abnormal amounts. As explained in the text, in many cases determinations for urobilin were not done.

* In this column, ♂ indicates male, and ♀ female.

ducts. The remaining fifteen for various reasons did not undergo operation, but were discharged from the hospital with a flat diagnosis of cholelithiasis. They were seen by both medical and surgical consultants, who in every case agreed as to the diagnosis.

The results of the examination of the duodenal contents are given in Tables 3, 4 and 5. In Table 3 is given a summary of the findings in both groups of cases, together with the proportion of positive findings by history, physical examination and roentgen ray. Table 4 gives in detail the findings in the patients that came to operation, with a brief note as to any additional findings of interest. The results obtained in the unoperated patients are given in full in Table 5.

Before discussing the results obtained in this series of cases it is important to point out one essential difference between the findings here presented and those included in Table 2. In the previous group of pathologic controls, any sediment was considered abnormal that contained even rare amounts of either bile-stained cells or crystalline elements. In the present group of fifty-seven patients, no sediments

TABLE 5.—*Findings in Unoperated Gallstone Cases*

						Duodenal Sediment			Pigments			
Case	Sex	Age	History	Physical Examination	Roentgen Ray	Cholesterin	Bilirubin	Bile-stained Cells	Urobilinogen	Urobilin	Bilirubin	Discharge Diagnosis
43	♀	49	Pos.	±	Ques.	+	++	..	0	—	38	Cholelithiasis
44	♀	54	Pos.	Neg.	Ques.	++	+	..	8	—	430	Cholelithiasis
45	♀	70	Pos.	Pos.	Pos.	..	++	+	8	—	216	Cholelithiasis
46	♀	59	Pos.	Pos.	Neg.	..	+++	..	0	—	180	Cholelithiasis
47	♀	40	Pos.	Pos.	Neg.	+	++	..	—	—	...	Cholelithiasis
48	♂	69	Pos.	Pos.	Neg.	..	+++	..	0	—	40	Cholelithiasis
49	♂	16	Pos.	Pos.	Neg.	++	..	..	0	—	150	Cholelithiasis
50	♂	55	Pos	Pos.	Neg.	..	+	+++	0	—	40	Cholelithiasis
51	♂	39	Pos.	Pos.	Ques.	+	+	..	0	—	150	Cholelithiasis
52	♀	34	Pos.	Pos.	Neg.	+	++	..	0	—	131	Cholelithiasis
53	♂	53	Pos.	Pos.	Not done	..	++	..	T	—	170	Cholelithiasis
54	♀	51	Pos.	Ques.	Ques.	..	++	++	0	—	240	Cholelithiasis
55	♂	55	Pos.	Pos.	Not done	..	++	++	0	—	80	Cholelithiasis
56	♀	35	Pos.	Ques.	Ques.	..	+	..	0	16	150	Cholelithiasis
57	♂	72	Pos.	Pos.	Ques.	++	++	+	4	—	200	Cholelithiasis

The signs and symbols in this table are the same as those used in Table 4.

were considered of importance unless they contained easily recognizable amounts of one or the other element.

A brief description of the abnormal elements seen in the duodenal sediments under discussion is in order at this time. "Bile-stained cells" consisted either of leukocytes or of epithelial cells; the latter were round or columnar, and not infrequently whole layers of yellow columnar epithelium were observed, often in fan-shaped arrangement.

The abnormal crystalline elements, to which particular attention was paid, consisted in typical cholesterin plates, amorphous yellow bilirubin, and the darker yellow-brown granular crystals of calcium bilirubinate. As is to be seen in the tables, the individual crystalline elements were found alone, or in combination with each other. As a rule the bile pigment crystals were composed of both types before mentioned, and are given together in Table 3. The accompanying illustration was prepared from a typical duodenal sediment obtained in a case of chole-

lithiasis, and shows all three crystalline elements. It was not at all uncommon to find conglomerate masses of cholesterin and pigment crystals, apparently very early stones in the making. In a typical case it was usual to find several large masses of abnormal crystals, as well as several smaller clumps, in one cover-glass preparation.

Numerous other crystalline forms were also observed, but were not sufficiently characteristic to warrant classification. It is of interest, in view of the recent work of Rous, Drury, and McMaster[22] on the experimental formation of gallstones in animals, that frequently, in cases of gallbladder disease, masses of substances were observed which corresponded to the calcium carbonate crystals in the form of "speroliths" or other shapes noted by these workers. Atypical cholesterin plates with pigment nuclei were also observed. The granular forms of calcium bilirubinate corresponded almost exactly to the "pigment nuclei" described by the foregoing authors. It is important, in this connection, to comment on the identification of the bile pigment crystals. Low power examination is usually sufficient to establish the identity of these crystals on account of the intensity of the yellow color. Degenerated biliary tract cells may, on casual examination, simulate the amorphous bilirubin crystals, but a careful glance under high power will readily distinguish between the two.

Examination of Table 3 indicates that in all but one of the fifty-seven patients, abnormal crystalline sediments were found. Thirty-two of these sediments, or 56 per cent., showed large clumps of bile pigment crystals; twenty patients, or 35 per cent., showed a combination of cholesterin and pigment crystals; and four patients, or 7 per cent., showed only pure cholesterin. It is of interest to note that, in the patients undergoing operation, the three having pure cholesterin sediments showed practically pure cholesterin stones at exploration. In the majority of the remaining patients the stones were composed of cholesterin and bile pigment. In one patient with hemolytic jaundice (Case 16), pure pigment stones were found, corresponding exactly to the material obtained by duodenal drainage.

Of the fifty-seven patients, only one failed to show definitely abnormal amounts of crystals in the duodenal sediment. This patient (Case 41) did show rare clumps of bilirubin, and a very large amount of bile-stained columnar epithelium.

Twenty-one of the patients with cholelithiasis, or 37 per cent., in addition to abnormal crystalline elements showed grossly abnormal amounts of bile-stained cellular material.

22. Rous, P.; Drury, D. R., and McMaster, P. D.: Observations on Some Causes of Gallstone Formation, J. Exper. Med. **26**:77, 1924.

COMMENT

Analysis of the above figures shows clearly that in this unselected group of fifty-seven cases of cholelithiasis, practically all showed, on duodenal drainage, a sediment containing, in abnormal amounts, those crystalline elements chiefly concerned in the formation of gallstones. In addition, about one-third showed evidence of some biliary tract inflammation, as evidenced by the appearance of large numbers of bile-stained cells. Any attempt to localize the seat of stone formation, or of the irritative process by examination of the sediment, however, would be as fallacious as an attempt to localize genito-urinary pathology by examination of the urinary sediment.

A study of the foregoing results, and comparison of them with the data given in the group of other pathologic conditions (Table 2), would seem to indicate that in cases of cholelithiasis the duodenal sediment will reveal characteristic findings. In other pathologic conditions involving the biliary tract, the duodenal sediment may frequently show abnormal cellular or crystalline elements.

In any condition involving the biliary tract, it should be noted also that "casts" of bile-stained material are of frequent occurrence. They have been described by many observers, but are of little significance unless seen in abnormal numbers, as they are often found in normal duodenal sediments. A good description, together with illustrations of such "casts" or "bile thrombi," may be obtained in the article already alluded to, by Rous, Drury and McMaster.[22]

The main point of difference between the findings in cases of cholelithiasis and those in other diseases of the biliary tract, lies in the almost constant occurrence of large amounts of abnormal crystalline elements. I consider this point to be of real diagnostic significance.

The object of this investigation has been to ascertain, first, the constancy with which typical findings may be obtained by duodenal drainage in certain diseases, and second, to determine whether the results thus obtained warrant the use of the method as a diagnostic procedure. In another paper the writer has already shown the characteristic findings in infectious (catarrhal) jaundice. Similarly, examination of Tables 3, 4 and 5 indicates that in nearly all cases of cholelithiasis there is a typical set of findings, provided the proper technic is employed in the sedimentation of the duodenal contents. The additional finding of abnormal bile pigment values is suggestive but not diagnostic of biliary tract pathology. Other types of liver disease, as shown in data in Table 2, do not give constant results by duodenal drainage. The occurrence of such findings as those noted in Table 2, however, are strongly suggestive evidence of biliary pathologic changes, but are not diagnostic of any single disease entity.

The practical value of the method as a diagnostic procedure is indicated in Table 3. Of the fifty-seven patients with gallstones, five gave questionable histories, six gave absolutely misleading histories, and in three there was an entirely negative story. Thus, in nearly 25 per cent. of the group, a carefully taken history was of little or no value. Similarly, in about 45 per cent. of the patients, physical examination was of little or no value, and in two cases was absolutely misleading. Roentgen-ray examination was not performed on every patient, but of the forty-seven patients so studied only twenty-two, or about 45 per cent., suggested gallbladder pathologic changes. It is evident, therefore, that in an unselected group of cases of cholelithiasis, routine methods of examination are far from being infallible. Comparison of these data, with the findings made by duodenal analysis, would seem to indicate that a much higher percentage of positive results was obtained by the latter method than by the methods of diagnosis usually employed. It is far from being my intention to make fantastic claims for a method that has already been severely criticized because of immature and unwarranted assertions made in its behalf. It would seem, however, that by strict adherence to a relatively simple technic, duodenal analysis promises much of value in diagnosis of diseases of the biliary tract, and particularly in the diagnosis of cholelithiasis. The very high proportion of positive findings in fifty-seven cases of cholelithiasis may have been fortuitous, and a similar analysis of a much larger series might show more negative results. It is my opinion, however, based on the foregoing data, and after examination of a large number of specimens of bile obtained at operation from the gallbladder or bile ducts, that abnormal crystalline elements are nearly always to be found in the presence of biliary calculi. I believe, therefore, that duodenal analysis is of real diagnostic value, in spite of the time consumed, and the discomfort incident to the performance of the test. Like any laboratory test it is subject to error, and should not be employed in the place of ordinary and well-tried methods of examination. On the contrary, the only valid excuse for its existence is that it may be used as an additional diagnostic procedure.

The unfortunate manner in which the method has been employed by some physicians as a diagnostic and therapeutic measure for all ills, directly or indirectly related to the biliary tract, is greatly to be regretted. Unproved hypotheses have been welcomed by a few without due consideration for proper experimental evidence, and apparently have been used only as a basis on which to build a larger consultation and "special" practice. The psychologic effects produced by duodenal drainage have undoubtedly led, in some cases, to methods closely approximating charlatanry. It is to be hoped that the medical profession at large will assign to this procedure its proper place. It is, I believe, of undoubted

value, both as a therapeutic and diagnostic measure, but only in a selected group of cases, and only when performed in an intelligent and careful manner.

SUMMARY AND CONCLUSIONS

1. The results of duodenal analysis in 274 cases is here reported. In addition to normal controls, 202 pathologic controls have been studied, including twenty-seven different disease entities. Fifty-seven cases of cholelithiasis have also been studied, in forty-two of which the diagnosis was proved by operative findings.

2. Analysis of the duodenal contents in these cases has consisted in spectroscopic estimations of the various bile pigments, and in the microscopic examination of the duodenal sediments for abnormal cellular and crystalline elements.

3. The importance of high-speed centrifugalization of the duodenal contents has been emphasized as the only means of securing consistent sediment findings.

4. Abnormal sediment findings have been found to consist of bile-stained epithelium or leukocytes, and cholesterin, bilirubin or calcium bilirubin crystals.

5. In cases of cholelithiasis, characteristic sediments have been found. These findings consist of abnormal amounts of any or all of the above named crystalline elements. Bile-stained cellular elements which are interpreted as suggestive of an irritative process in the biliary tract, are also found in a large proportion of these cases.

6. Other types of biliary tract disease, as a rule, also exhibit abnormal cellular or crystalline elements, but with no degree of constancy, and the findings in such cases are suggestive, rather than diagnostic. This statement is of particular interest in a differential diagnosis between chronic cholecystitis and cholelithiasis.

7. The results of bile pigment estimations in the cases studied tend to confirm previous investigative findings. As a rule, these estimations are definitely increased over normal in cases of increased blood destruction or in cases with functional disturbance of the liver.

8. The diagnosis and treatment of biliary tract disease by duodenal drainage, on the theory that magnesium sulphate instillations into the duodenum produce gallbladder contractions and subsequent drainage, is criticized, on the basis of clinical and experimental observations. Deductions as to the localization of biliary tract pathologic changes on the basis of so-called "A," "B" and "C" biles are similarly criticized.

9. A conservative use of duodenal analysis as a therapeutic and diagnostic measure in carefully selected cases is advocated.

TREATMENT OF ASTHMA WITH AUTOGENOUS VACCINES*

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It has been recognized that the greatest stumbling block in the treatment of asthma is infection and, until some method is developed which may be a guide to vaccine therapy its results will be uncertain. No authoritative work has appeared in the literature to solve this difficult problem. In fact, marked difference of opinion still exists regarding the rôle played by bacteria in the causation of asthma and the value of vaccines in its treatment.

No theory is here offered as to the cause or the relief of asthma, but we do wish to present a clinical method of study and treatment which has appeared to produce in a small series of cases a large percentage of favorable results. We have attempted to free our minds of preconceived ideas and prejudices and to examine the question from the clinical point of view, submitting the method to the verdict of result obtained.

Sixty-two cases of asthma and asthmatic bronchitis, tested and treated with autogenous vaccines in the asthma clinic of St. Luke's Hospital and in private practice, form the basis of this report. The method of testing with autogenous vaccines has been described elsewhere.[1] Before considering the advisability of treatment with vaccines we subjected all of our patients to a physical examination and to cutaneous tests for hypersensitiveness to foreign proteins. Where such hypersensitiveness was demonstrated in apparent causal relation to the asthmatic condition, an effort was made to separate the patient from the offending protein or, when indicated, to desensitize him. In many instances surgical treatment was obtained for gross obstructions in the nasal passages and nasopharynx, and for infected nasal sinuses, tonsils and teeth. In addition, some form of medication was prescribed, and some of these patients were put to bed at home or in the hospital.

During this preliminary period of observation and of symptomatic or specific treatment, which was rarely shorter than two weeks, a considerable number of patients were relieved of their asthma, and consequently did not receive vaccine treatment and are not included in this

* From the wards and asthma clinic of St. Luke's Hospital.

1. Thomas, W. S.: Famulener, L. W., and Touart, M. DeM.: This issue, page 85.

series. The remaining sixty-two cases were tested with autogenous vaccines and received therapeutic inoculations in accordance with the results of those tests. In all cases, ample opportunity was provided for remedial measures other than autogenous vaccines to produce a therapeutic effect before the latter were used.

In the preparation of test vaccines, cultures were made from various sources depending on the indications in each particular case. Where sputum was obtainable it was always used, as was also aspirated material from infected accessory nasal sinuses. Cultures were sometimes made from excised tonsils and directly from the nares, pharynx and the tonsils in situ. In certain instances, either because of some clinical indication or because of failure to obtain positive reactions with bacteria from other sources, cultures were made from the stool.

All organisms recovered from every source were made into vaccines, and with these vaccines intracutaneous tests were made and the readings interpreted as described in the paper before mentioned.[1]

It not infrequently happened that definite clinical improvement was noted within a few hours after the tests were made. In seven cases this amounted to complete and in three to complete and permanent relief. Vaccine treatment was begun as soon as possible after decisive information had been obtained from the tests, usually from three to five days. Occasionally, only one organism was chosen but it more often happened that two or more gave sufficiently active reactions to be included. The treatment vaccines were separate suspensions of each organism in physiologic sodium chlorid solution in water, plus 0.25 per cent. tricresol, each cubic centimeter containing approximately one billion organisms. At times, combined vaccines of two or more organisms were used. With some of the more toxic bacteria, notably *Streptococcus hemolyticus* and the Friedländer bacillus, the treatment dilution was reduced to five hundred million organisms in each cubic centimeter. The advantage in administering each type of organism separately is that it is then possible to judge accurately its effects by the size and severity of the local reaction.

In this method of vaccine therapy our purpose has been to produce in healthy tissue, at frequent intervals, a local reaction characterized by slight swelling and tenderness, and perhaps erythema of the overlying skin, lasting from one to five days. The initial dose was approximately one hundred million organisms of each treatment dilution, and if this dose produced such a local reaction it was repeated at intervals of two or three days until none followed. In the event of failure to produce a local reaction or when a previously sufficient dose ceased to cause such a reaction, the amount was increased by one hundred million organisms on each occasion until the desired result followed. It seldom happened that the dosage exceeded four hundred million organisms at any time

during the treatment. As the asthma improved, the interval between doses was increased first to five and later to seven days. Rapid and uninterrupted recovery occurred in a few patients, but the usual course was gradual improvement, varied from time to time by exacerbations of the asthma. In most of these patients vaccines were discontinued as soon as relief of symptoms and physical signs occurred. Finding, however, an occasional tendency to relapse after an interval of weeks or months, the more recent patients have been treated with weekly, bi-weekly or monthly doses long after the occurrence of clinical relief. In so doing we are in accord with a recently published statement of Rackemann,[2] to the effect that the prolonged use of vaccines appeared to prevent relapses. The duration of treatment varied from one to ten weeks and averaged about six weeks; the number of vaccine doses varied from one to thirty and averaged about fifteen. Where symptoms continued unabated after six or ten inoculations, fresh cultures were made, at times disclosing the presence of organisms hitherto undiscovered.

The important factors in the use of vaccines in our experience seem to be: (1)proper selections by the intracutaneous test; (2) preparation of each organism in a separate vaccine; (3) the use of a therapeutic dose just sufficient to produce a mild local reaction; (4) adherence to this dose so long as it continues to produce such a reaction, then increasing it; (5) frequent dosage early in the treatment with a gradually lengthened interval, followed by (6) prolonged administration at relatively long intervals.

REPORT OF CASES

CASE 1.—F. M., a man, aged 75, was admitted to the hospital, Jan. 23, 1923, complaining of cough with expectoration, and paroxysmal dyspnea of twenty years' duration, which had recently become so severe as to incapacitate him.

Physical Examination.—Emphysema, chronic bronchitis with asthma and myocardial insufficiency were the chief findings. Dermal tests for hypersensitiveness to food and air borne proteins were followed by negative reactions. Intracutaneous tests with autogenous vaccines made from sputum produced a sharp late reaction to *Staphylococcus aureus* and *Micrococcus catarrhalis*. Treatment was instituted with vaccines of these organisms administered every second day. The patient was discharged from the hospital February 20, completely relieved. On September 25, a letter was received stating that complete relief continued.

CASE 2.—J. B., a man, aged 77, was admitted to the hospital Jan. 16, 1923, complaining of cough and paroxysmal dyspnea for the last year, at first nocturnal but lately continuous. There had been no previous attack.

Physical Examination.—The findings were those of chronic bronchitis, with asthma and emphysema and myocardial insufficiency. The patient's mother was asthmatic and his father died of tuberculosis. Cutaneous tests with food and air borne protein were followed by negative reactions. Intracutaneous tests with vaccines of all the organisms isolated from the sputum produced both early and late positive reactions to *Staphylococcus aureus* and *Bacillus coli communis*. Vaccines from these, in proper dilution, were consequently administered at intervals of two days until April 2, when he was discharged completely relieved.

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2. Rackemann, F. M.: J. Immunology, August, 1923.

He returned to the hospital November 18, stating that he had suffered from a relapse for the last three weeks. A new bacterial flora was isolated from his sputum, and when tested sharp late positive reactions to *Streptococcus viridans*, strain 3, and *Micrococcus catarrhalis* were obtained. He likewise reacted sharply to a stock *Bacillus coli communis* vaccine. He was accordingly treated with the vaccines of these organisms with prompt relief of symptoms. He was discharged completely relieved December 12.

CASE 3.—M. S., a man, aged 38, had slight asthma from infancy, but for five months previous to November, 1922, had suffered severely and continuously and had lost 40 pounds (18 kg.) in weight and correspondingly in strength. He had received active treatment of various sorts, including autogenous vaccine therapy, in hospital, and was treated otherwise in several healths resorts without avail.

He was found to be sensitive to all available feather proteins and was carefully removed from contact with them without obtaining relief.

His sputum on culture yielded pneumococcus type 3, *Staphylococcus albus* and *Streptococcus viridans*. He reacted actively both early and late to the pneumococcus and received therapeutic inoculations with the same. Prompt improvement occurred and on again removing him from contact with feathers, the patient experienced complete relief after two months of treatment. He was then able to sleep on a feather pillow again, and to live at home where he kept chickens and canaries.

A slight relapse occurred in October, 1923, at which time his left antrum was found to contain pus and was washed out. The material yielded *Micrococcus catarrhalis*, staphylococcus and pneumococcus, Group 4. The pneumococcus could not be grown sufficiently to make a vaccine, but vaccines of the other organisms were prepared and he was tested with them but no reactions were obtained. The patient then received inoculations with the former vaccine; he experienced relief at once, and remains entirely free of asthma to date.

COMMENT

In classifying our results we have used the following terms: (1) relieved, denoting complete and at last report permanent relief; (2) markedly improved, denoting that subjectively and objectively the patient was relieved of most of his symptoms even though some asthma continued in the form of isolated paroxysms or as dyspnea on exertion or when exposed to irritating vapors, dust or wind; (3) recent, denoting that these cases are still under treatment and, though relieved or markedly improved, the final result is still undetermined; (4) failure, denoting those cases where relief was slight or temporary or where no improvement occurred.

The result of the whole series is shown in Table 1. Of sixty-two patients treated, thirty-two, or 51.6 per cent., are completely relieved of

TABLE 1.—*Asthma and Asthmatic Bronchitis Tested and Treated with Autogenous Vaccines*

	Number		Per Cent
Relieved	32	or	51.6
Much improved	14	or	22.6
Recent, relieved under treatment	8	or	12.9
Failures	8	or	12.9
Total	62	or	100.00

their asthma; fourteen, or 22.6 per cent., are markedly improved; eight, or 12.9 per cent., are recent, and eight, or 12.9 per cent., were failures.

Advanced age did not appear to be an important factor in the prognosis. In Table 2 the sixty-two cases are arranged in age groups. Our

TABLE 2.—*Ages and Results, Sixty-Two Cases of Asthma and Asthmatic Bronchitis Tested and Treated with Autogenous Vaccines*

	Age Groups			
Results	1 to 20 Years 7 Cases Pr. Ct.	21 to 40 Years 19 Cases Pr. Ct.	41 to 60 Years 27 Cases Pr. Ct.	61 to 80 Years 9 Cases Pr. Ct.
Relieved	57	36	55	66
Much improved	0	26	22	33
Recent, relieved under treatment	28	16	11	0
Failures	14	21	11	0

youngest patient was aged 7 years and completely relieved, and our oldest was 77 years and completely relieved. Sixty per cent. of these sixty-two patients were over 40 years of age, and there were nineteen between 50 and 60 years.

In Table 3, the thirty-two completely relieved patients are grouped according to the duration of their asthma. Long duration of the asthma

TABLE 3.—*Duration of Asthma in Thirty-Two Cases Completely Relieved After Treatment with Autogenous Vaccines*

Duration	Number of Cases
1 year or less	1
1 to 5 years	19
6 to 10 years	6
10 years or longer	6

did not seem to influence the result unfavorably. For example, two of these patients were asthmatic from infancy. They were aged 38 and 50 years respectively.

Table 4 shows the duration of relief in the same thirty-two cases. As indicated in the footnote, six of them have had relapses but were

TABLE 4.—*Duration of Complete Relief in Thirty-Two Cases of Asthma Treated with Autogenous Vaccines* *

Duration	Per Cent.
1 month	3.00
2 to 6 months	37.5
7 to 12 months	40.7
13 to 18 months	9.4
Not followed	9.4

* Six patients relapsed but were promptly relieved after further vaccine treatment.

promptly relieved after further vaccine treatment. Nineteen were examined during the month in which this was written, three during the previous month, six at various intervals back to five months before, one died from apoplexy after five months of entire relief and three were not traced.

Eight failures are reported. Of these, four are now under observation for further study, and individually present the following conditions which may have contributed to the failures:

Case 1.—Unresolved interlobar pleurisy and radiographic evidence of pulmonary tuberculosis.

Case 2.—Purulent bronchitis, yielding organisms in the sputum not previously recovered in our cultures and consequently not used in tests and treatment.

Case 3.—Purulent pansinusitis with nasal polypi and a new bacterial flora in the sputum.

Case 4.—Clinical and radiographic evidence of pulmonary tuberculosis.

Of the remaining four, whom we have not been able to follow, one had, when last seen, purulent ethmoditis with nasal polypi, unrelieved by surgical treatment and vaccines.

SUMMARY

1. The reactions to intracutaneous tests with autogenous vaccines were studied in sixty-two patients with asthma and asthmatic bronchitis.

2. These sixty-two cases received therapeutic inoculations with autogenous vaccines selected in accordance with the results of these tests.

3. In 12.9 per cent. no improvement was obtained, but complete relief or material improvement followed in 87.1 per cent.

AUTOGENOUS VACCINES IN DIAGNOSIS, WITH SPECIAL REFERENCE TO ASTHMA*

PRELIMINARY REPORT

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AND
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Specific reactions by the human skin to certain organic substances are important aids in diagnosis. Skin tests with air borne and food proteins, as guides in determining the exciting causes of asthma and allied disorders, have found a place in company with the Schick, the luetin and the dermal tuberculin tests. Less attention has been directed toward tests with bacterial vaccines in the infected and hypersensitive patient; indeed, their importance has been questioned. A few investigations in vaccine skin testing have been published by others, who report suggestive but confusing results. The difficulties encountered in making an adequate study of this problem from the bacteriologic standpoint have, perhaps, accounted for some of the earlier failures.

On beginning the study of a case of asthma or allied disorder, air borne and food proteins as etiologic factors should be eliminated, if possible, by proper skin tests. Positive skin reactions to one or more of these proteins are encountered in a little over one-half of all patients thoroughly tested. In the event of a complete series of protein tests with negative reactions, or in case of failure to relieve symptoms by treatment, as indicated by the reactions, a bacteriologic survey of the case should be undertaken. Asthmatic patients have been encountered who were hypersensitive to food or air borne proteins, but who were not completely relieved of their symptoms when separated from their offending proteins. Several of them were found to give positive skin reactions to autogenous vaccines, and were entirely relieved by vaccine treatment as indicated by the reactions to vaccine tests. These patients were apparently hypersensitive to bacterial proteins as well as to those of foods or those air borne.

The basic requirement is a thorough and most exacting bacteriologic examination of materials from all possible foci of infection. Attention is chiefly directed to a study of materials from the nasal cavity and accessory sinuses (in particular, the ethmoids and antrums); infected adenoids; tonsillar material from the crypts; pus, if present; sputum from the deeper air passages (Table 1); also the feces.

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* Read before the New York County Medical Society, Dec. 19, 1923.

Besides the four principal foci (nasal cavity with accessory sinuses, tonsils, lungs, intestinal tract), other possible sites should be considered, such as apical abscesses of the teeth, gallbladder infection (duodenal contents), infected endometrium, seminal vesicles, prostate and urinary tract. The clinician, in the physical examination of his patient, should search for all possible foci of infection. Material from infected foci should be collected and submitted to the bacteriologist for the isolation and identification of organisms present.

The methods employed in the collection of material for bacteriologic examination have a considerable bearing on final results. Great care should be exercised to exclude extraneous contaminants and an aseptic technic is essential in all cases. Nasal discharges may be collected with

TABLE 1.—*Incidence of Bacteria Found in the Sputum of 180 Patients Examined*

	Times
Streptococcus viridans	311
Chromogenic coccus	62
Staphylococcus aureus	51
Staphylococcus albus	50
Streptococcus hemolyticus	42
Atypical gram-negative coccus	34
Atypical gram-negative bacillus	30
Pneumococcus	25
Micrococcus catarrhalis	13
Streptococcus indefinite	12
Enterococcus	11
Bacillus coli communis	9
Bacillus fecalis alkaligenes	9
Micrococcus albus	8
Staphylococcus aureus hemolyticus	7
Bacillus Friedländer	4
Staphylococcus albus hemolyticus	3
Staphylococcus citreus	3

sterile cotton swabs, or, if copious, in sterile gauze wipes. Tonsillar exudate or pus may likewise be collected on sterile cotton swabs, care being taken to prevent contamination with saliva. If it is impracticable to make cultures at once, the swabs containing the material should be replaced in the sterile test tube, plugged with a sterile cotton stopper and sent to the laboratory to be immediately cultured. Sputum or feces should be collected directly in sterile jars and placed on ice, if it is impossible to culture at once. In private practice, material collected on sterile cotton swabs may be seeded at once on the surface of solid culture mediums (blood agar slants and Loeffler's serum medium) and sent immediately (with collecting swab in sterile plugged test tube) to the bacteriologic laboratory for examination.

It is essential in the bacteriologic examination of specimens that a careful study of stained films of the original material is made, as a

guide to the bacterial flora present, and that it be cultured on special or enriching mediums, as indicated. Further, the study of stained films of the original material offers a means of determining whether or not all types of organisms present develop later in the cultures. If not, further attempts should be made to culture and isolate all organisms that were found in the original material. Types of organisms not found at first are occasionally obtained by subsequent cultures of new material from the same source. The recurrence of symptoms in a treated case, after a quiescent period, calls for a repetition of the full bacteriologic examination in order to determine if infection with other types of organisms has supervened.

As a routine laboratory procedure, the materials are cultured directly on human blood agar slant and in dextrose nutrient broth; also a portion is emulsified in broth from which seedings are made by the dilution method in a series of poured blood agar plates. After the proper period of incubation has elapsed, stained preparations are made of the organisms which have developed from the original cultures in the blood agar slants and in the dextrose nutrient broth inoculations. The organisms present are carefully studied microscopically to identify the types, and steps are taken then for the isolation and cultivation of each species or strain. The primary blood plates are examined especially for hemolyzing types of organisms, and fishings from colonies are transferred to suitable culture mediums.

After cultivation, isolation and identification of the bacterial strains present in a given specimen, it is necessary to prepare vaccines both for testing and for therapeutic purposes. Without going into full details of the technic of culturing and killing organisms usually employed in the preparation of a bacterial vaccine, it is sufficient to state that the organism is ordinarily cultured either on plain nutrient agar slants or in dextrose nutrient broth, dependent on the particlar species. Ultimately they are killed by heating for one hour at 60 C., or at 65 degrees, if necessary.

The standardization of the vaccine is based on the method published by Hopkins.[1] The Hopkins method offers a means by which an accurate measurement by volume of the thoroughly packed moist organisms may be made in a special type of centrifuge tube. A 1 per cent. suspension in physiologic sodium chlorid solution is prepared from the measured packed bacterial residue; then the organisms are killed by heat. Controls for sterility are made, after which sufficient tricresol solution is added to give an 0.25 per cent. concentration. Instead of standardizing the original 1 per cent. suspension by determining the number of organisms

1. Hopkins, J. G.: A Method for Standardizing Bacterial Vaccines, J. A. M. A. **60**:1615 (May 24) 1913.

present in 1 c.c., as advised by Hopkins, a unit valuation has been placed on the volume content of bacterial substance present in such a suspension. The unit consists of that amount of bacterial substance which is present in 0.01 c.c. of a 1 per cent. suspension of the organism prepared under certain fixed conditions.[2] Experience has shown that this quantity (one unit) of vaccine is, perhaps, the most favorable amount to produce a skin reaction when applied intradermally in the hypersensitive patient. The 1 per cent. suspension of killed organisms, prepared by the Hopkins method, is designated "vaccine stock," and is supplied in small ampules for the intradermal tests. The vaccines for therapeutic purposes are prepared from the "vaccine stock" which contains 100 units per cubic centimeter. Dilutions in physiologic sodium chlorid solution containing 0.25 per cent. tricresol are made to include the number of units per cubic centimeter desired by the clinician.

In establishing a vaccine unit, based on a known amount of bacterial substance present in a suspension, an attempt has been made to obtain (1) uniformity in dosage, (2) comparable valuations of vaccines prepared from different species of organisms and (3) constant valuation for vaccines made from the same bacterial species. Experience has shown that by the commonly employed methods of counting, inaccuracy in results may occur. Emphasis must be placed on the exacting technical character of the laboratory work, which demands the best efforts of a highly trained bacteriologist. (The clinician's success in diagnosis and treatment of the class of patients under consideration here is dependent on the full cooperation of the laboratory specialist.)

Each test injection is made with a freshly sterilized tuberculin syringe and a needle of fine caliber, with which the control solution and each vaccine are introduced intradermally, so that minute wheals are seen. The amount of test vaccine used in each instance is regularly 0.01 c.c. The scratch or dermal tests made with so-called proteins prepared from bacteria have been tried and have been found to be unsatisfactory.

As a control, in each series of tests, the same dilutent of sodium chlorid and tricresol solution is used as that employed in diluting the vaccines. The injections are made in a row, usually on the arm or forearm, which traverses the limb in a spiral direction, the distance between the points being at least 1½ inches (3.30 cm.). The oblique line is preferred because of the occurrence, in about 4 per cent. of the cases, of a reaction severe enough to cause a transitory lymphangitis producing a pink flush extending for several inches up the limb. Should this erythematous area cross another point of injection the result would be confusing.

2. This phenomenon occurred in 4 per cent. of the positive late reactions.

The positive reactions following these tests are of two separate types: (1) an early reaction, appearing in from ten to thirty minutes and soon thereafter fading; (2) a late positive reaction, noticeable in twelve hours or less, and at its height on the second day. It persists for from two to five days, and, under certain circumstances, for several weeks.

1. The early positive reaction is a wheal at least 1 cm. in diameter, with pseudopodia or grossly irregular outline, sharply marked off from a surrounding pink areola. Early positive reactions have been observed in thirty-five of 134 asthmatic and hay-fever patients (about 25 per cent.), but are rarely seen in other than this type of patient (Table 2). The majority of these 134 patients were nonsensitive to skin tests with air borne and food proteins.

TABLE 2.—*Organisms from All Sources Causing Early Positive Skin Reactions (Wheals with Pseudopodia) in 44 Out of 180 Patients Tested*

	Times
Staphylococcus aureus	12
Streptococcus viridans	11
Chromogenic coccus	8
Staphylococcus albus	6
Pneumococcus	5
Atypical gram-negative bacillus	4
Bacillus coli communis	4
Streptococcus hemolyticus	4
Micrococcus catarrhalis	3
Bacillus Friedländer	1
Bacillus fecalis alkaligenes	1
Bacillus typhosus	1
Enterococcus	1
Staphylococcus citreus	1

2. The late positive reaction is not unlike the Schick reaction in appearance, but in order to read and interpret its significance, the component features must be noted by touch as well as by sight, and recorded graphically, as they change from day to day. The chart enables one to decide which, if any, of the organisms used in testing should be employed in treating the patient.

COMMENT

Any of the following features may appear about the point of injection during the first twenty-four hours and may persist for five or more days following the test: (1) an indurated, slightly elevated nodule, usually about 0.5 cm. in diameter; (2) redness of the skin over the nodule; (3) a surrounding pink flush or zone of erythema, from 1 to 10 cm. in diameter, the so-called areola; (4) tenderness on pressure, usually occurring at the nodule only, but sometimes extending over the

whole areola; (5) heat, felt by the palpating finger; (6) lymphangitis,[3] lasting from one to three days, not necessarily associated with a pustule, but commonly with enlarged, tender glands; (7) slight fever and malaise occasionally accompany marked late positive reactions; (8) pustule.[3]

Late reactions to the different types of organisms vary somewhat. Staphylococci and streptococci regularly, but the intestinal group of bacilli less often induce the indurated nodule. Positive reactions to

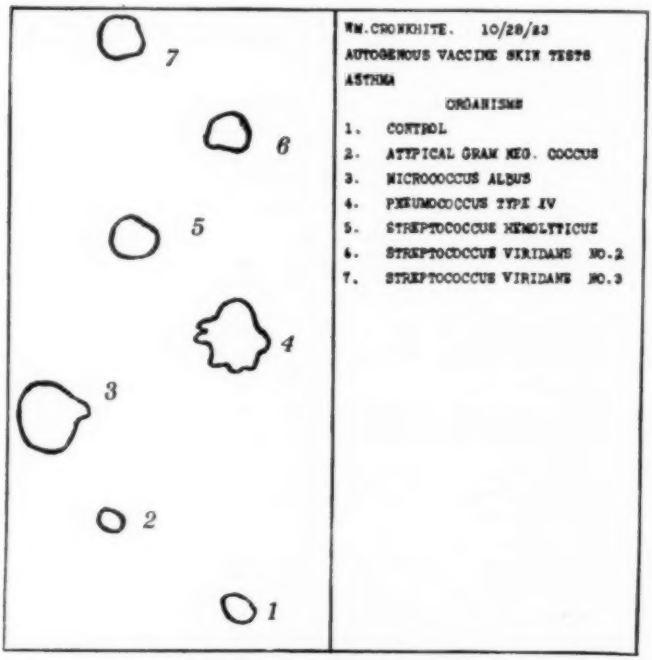

Fig. 1.—Early (half hour) reactions, as recorded in the text.

bacilli of the colon-typhoid group give large, hot areolae which fade in two or three days or more. The nodules caused by streptococci frequently persist for many days, or even weeks, sometimes becoming pigmented and occasionally showing desquamation.

Positive reactions, whether early or late, are considered to be of equal importance as indications for the therapeutic use of the vaccines which produced them.

3. A small sterile pustule at the point of injection was observed in about 4 per cent. of those patients who gave late positive reactions. Rarely has it been associated with a small slough.

In reading and recording the early reactions, the circumference of the wheal is outlined on the skin with pen and ink, and numbered. When dry, this picture is transferred to wet blotting paper laid on it (Fig. 1) and later filed for record.

Those features comprising the late reactions are recorded in charts as shown in Figure 2, A and B, in which N denotes an indurated nodule 0.5 cm. in diameter, two N's *vertically placed*, a nodule twice as large; R denotes redness at point of injection; RR, a deeper red color; T denotes tenderness on pressure; TT, exaggerated tenderness; A denotes a surrounding areola 1 cm. in diameter; AA, an aerola 2 cm. in diameter, etc.

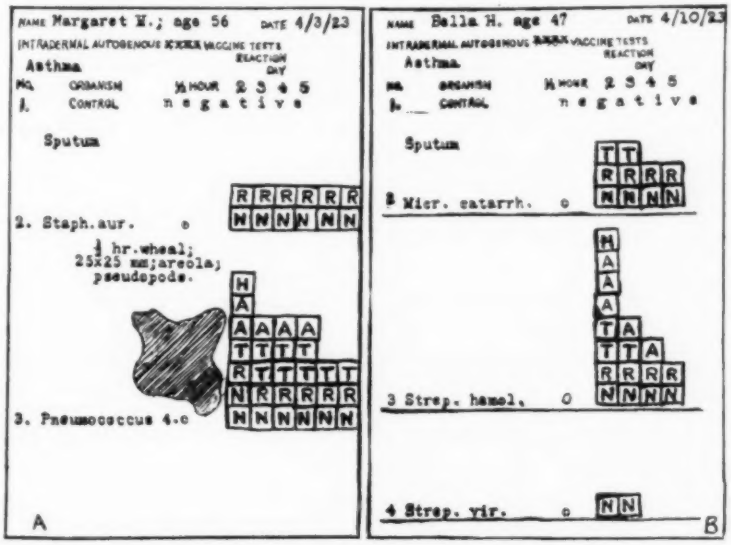
NAME Margaret W.; age 56 DATE 4/3/23
INTRADERMAL AUTOGENOUS VACCINE TESTS
Asthma
REACTION DAY
NO. ORGANISM ½ HOUR 2 3 4 5
1. CONTROL n e g a t i v e
Sputum
2. Staph.aur. o
½ hr.wheal; 25X25 mm;areola; pseudopods.
3. Pneumococcus 4.o
A
NAME Bella H. age 47 DATE 4/10/23
INTRADERMAL AUTOGENOUS VACCINE TESTS
Asthma
REACTION DAY
NO. ORGANISM ½ HOUR 2 3 4 5
1. CONTROL n e g a t i v e
Sputum
2 Micr. catarrh. o
3 Strep. hemol. o
4 Strep. vir. o
B

Fig. 2.—*A*, early positive reaction to pneumococcus, type 4; moderate late reaction to *Staphylococcus aureus*, and marked late positive reaction to pneumococcus. *B*, late positive reaction to *Streptococcus hemolyticus;* negative late reactions to *Micrococcus catarrhalis* and *Streptococcus viridans*. All early (half hour) reactions are negative.

(such areolae sometimes reach a diameter of 10 cm.); H denotes heat of nodule or areola as felt by the palpating finger; P denotes pustule; G denotes enlarged glands and includes lymphangitis.

Observations of the findings must be recorded daily over a period of at least five days, if persisting (Fig. 2).

SUMMARY

A late reaction is considered to be positive when, in addition to the features of the control injection, it exhibits during a period of five

days or longer, two or more of the before mentioned component parts. A positive reaction is not what appears at any one time, but is the aggregate of what is seen and felt at the site of the test during the five or more days following it. Such a chart as is shown in Figure 2 affords an efficient and almost indispensable means of depicting all of each reaction's features as they come and go.

A negative skin reaction to an autogenous vaccine is taken to indicate that the organism is innocuous to its host. However, vaccines made of organisms commonly considered to be nonpathogenic have often produced positive skin reactions, and when used in treatment have given relief of symptoms. It is evident, therefore, that test vaccines should be prepared from all types of organisms recovered from the patient.

Overdoses of vaccines, either in testing or treatment, have been followed by asthmatic seizures in ten of our patients, and in one of them on three occasions. A phenomenon not infrequently observed following the injection of a treatment vaccine is the lighting up of faded test reactions to the same bacterium.[4]

Studies in this field during the last three years have yielded sufficient data to encourage the belief that by means of preliminary skin testing, properly conducted, vaccine therapy may be put on a firmer footing. It is believed that by this method it may be possible to decide which of several autogenous vaccines should be used in treatment, or whether any vaccines should be used. False hope of cure by autogenous vaccine treatment in cases which show no positive reactions is averted. That these positive skin reactions to vaccines are not chance phenomena has been indicated by the positive results of repeated tests on the same person, and especially by the favorable results of vaccine treatment conducted in accordance with them. Of sixty-two patients suffering with asthma so treated, fifty-three have been either completely relieved or materially improved.

NOTE.—Autogenous vaccine skin tests and treatment have been conducted by the authors during the last two years on patients suffering with perennial hayfever, intestinal infections, arthritis, eye infections, dermatoses and pneumonia. It is planned to publish the work and its results in the near future.

St. Luke's Hospital.

4. Such a recurring reaction in one patient eventually formed a sterile pustule.

A CASE OF PELLAGRA—ITS BEARING ON THE ETIOLOGY AND CURE OF THE DISEASE

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It seems to have been fairly well established that poor or insufficient food, per se, does not cause pellagra. The epidemiologic observations of Goldberger [1] in 1914 furnish rather conclusive evidence that the disease is not bacterial in origin or transmissible by insect bites. To quote from Goldberger: "The investigations of the Public Health Service now permit one to answer the oft-repeated question: 'Is pellagra catching?' in the negative. No germ that can properly be considered the cause of the disease has ever been found. Attempts to give persons pellagra by inoculations of the blood, saliva, or other body discharges from several cases of pellagra have failed completely. . . . Furthermore, in an asylum where many of the inmates developed pellagra year after year, it was observed that the nurses and helpers who lived with them never developed the disease."

The work of White [2] and of Stannus [3] in which both observers were able to eradicate pellagra, in the first instance from a camp of Armenian refugees, and in the latter instance from the Central Prison of Nyasaland, by changing the diet only, all other conditions remaining the same, also points against its bacterial origin. It seems reasonably certain, therefore, that in pellagra we are not dealing with a disease caused by bacteria. Just what dietary factors are involved in the causation of pellagra has not been fully determined. As far back as 1866, Roussel (cited by Goldberger) ascribed to milk a very important place in its prevention. Lombroso [4] taught that a diet rich in meat was valuable in the prevention and cure of pellagra.

An epidemiologic study of the disease by Goldberger, Waring and Willets in an orphanage at Jackson, Miss., in 1915, disclosed the fact that only inmates between the ages of 6 and 12 years were affected. It was further observed that the diet of the affected group contained a disproportionately small amount of lean meat or other animal proteins. These investigators suggested at that time that prevention of the disease might be worked out if the diet were corrected to include more fresh meat, eggs, and milk. In order to test out further this conclusion, Gold-

1. Goldberger: Public Health Report Reprint, No. 461, 1914, pp. 6-7.
2. White: Report of an Outbreak of Pellagra Amongst Armenian Refugees at Port Said, 1916-1917.
3. Stannus: Tr. Roy. Soc. Trop. M. & Hyg., 1920, p. 16.
4. Lombroso: Die Lehre vonder Pellagra, Berlin, 1898.

berger and Wheeler,[5] in 1915, at the Mississippi State Penitentiary undertook to produce pellagra experimentally in eleven volunteer inmates of the prison by the exclusion of fresh meat, milk, and eggs. As a result of this experiment, six out of the eleven men showed symptoms distinctive of pellagra, while in thirty-five controls living under the same conditions, but allowed meat and milk, no case of pellagra was observed. The diet on which the eleven men were fed was not deficient in antineuritic, antiscorbutic, or fat soluble A vitamin, nor was it deficient in the quantity of food consumed. To quote the conclusions of these observers: "So that of the now generally recognized essential dietary factors there remain for consideration as possibly essential in relation to the etiology of pellagra, the protein (amino-acid) and the inorganic factor."

The studies of Osborne and Mendel,[6] McCollum [7] and his associates, and more recently Wilson,[8] confirm this view. That the protein element in the diet is an important factor is shown by the work of Goldberger, Waring and Willets [9] in their attempt to prevent the disease in the Georgia State Sanatorium and in two orphanages. Following modifications in diet to include more proteins, not one of seventy-two pellagrous persons in the Georgia institution developed evidence of a return of the disease. In one of the orphanages, in 172 pellagrous children there was only one recurrence, and in the other orphanage not a single case appeared in 168 nonpellagrous inmates. These observations were made over a year's interval of time. In studies derived from clinical experience, it is important that evidence bearing on this protein deficiency conception of the disease should be published.

The following case which I report should be placed on record, first, because it supports the defective protein theory relative to the etiology of the disease, in that the patient had been deprived of meat for about two years prior to the onset of the attack; second, because of the prompt recovery on a generous meat diet and the use of sodium cacodylate intravenously, and, third, because it is the first case to be reported from South Dakota, a supposedly nonpellagrous area.

REPORT OF CASE

Mrs. E. B., aged 50, married, the mother of three children, living at Mellette, S. D., was referred by Drs. Kleger and McCauley, March 29, 1923, complaining of nervousness, soreness of the mouth, diarrhea, and a dirty brown rash over

5. Goldberger, Joseph, and Wheeler, G. A.: Experimental Pellagra in White Male Convicts, Arch. Int. Med. **25**:451 (May) 1920.
6. Mendel, L. B.: Nutrition and Growth, J. A. M. A. **64**:1539 (May 8) 1915.
7. McCollum, E. V.: J. A. M. A. **71**:937 (Sept. 21) 1918.
8. Wilson: Hygiene **20**:1-59, 1920.
9. Goldberger, J.: Waring and Willets: U. S. Public Health Reports **30**: 3117-3131, 1915.

Fig. 1.—Ventral view of the left hand of Mrs. K. B.

Fig. 2.—Dorsal view, left hand, same patient.

Fig. 3.—Ventral view of the right hand, same patient.

Fig. 4.—Dorsal view, right hand, same patient.

Fig. 5.—Mucous membrane of the lips, same patient.

the forearms and hands. The family history was negative. One sister had died of goiter. She had always been well until two years ago, when she had all her teeth extracted and had to live on soft, mushy foods. She could not get a good fitting plate and ate almost no meat. At Christmas, 1922, she was very nervous and felt as if she would "go to pieces." This feeling of exhaustion and weakness increased and in March, 1923, her mouth became sore, red, and hurt her when she chewed. About this time she began having seven or eight loose stools a day, and the rectum pained and burned. At this time also, the skin on the forearms, half way to the elbows, became dirty brown and scaly in appearance. The rash gradually extended to the backs of the hands and the fingers. She had never had anything like it before. All efforts to control the rash by local application failed. About two weeks after the rash appeared, the skin began to crack about the wrists. She had no headache but was confused in her mind and slow in her speech and thought. Her eyesight became blurred. She could not concentrate on whatever she was doing. The diarrhea had stopped about two weeks before the patient appeared for examination. She had lost in weight 25 pounds (11.3 kg.). She stated that she had lived in the town of Mellette, S. D., for the last forty years, that she had in no way changed her diet or mode of living until after the teeth were removed two years before, when she stopped eating meat and had eaten soft foods, such as milk toast, cream of wheat, potatoes, carrots, cabbage, bread and butter, cream, cooked fruits, grape fruit, soft puddings, cake and pie.

The examination revealed a fairly well nourished woman of rather stocky build. Her color was pasty white, somewhat suggestive of myxedema, chronic interstitial nephritis, or possibly early pernicious anemia. The pupils reacted to light and in accommodation. The knee jerks were active. There was no incoordination. Her speech was slow and her mental responses sluggish. The mucous membrane of the lips and gums and inside of the mouth and the tongue were fire red (Fig. 1). There was a fine, whitish exudate, like that accompanying the spirillum of Vincent infection, over the roof of the mouth and the jaws. This was easily wiped off. In places, the mucous membrane hung down in folds. A remarkable, crusty, dirty brown pigmentation and rash was present from about the middle of the forearms downward, extending over the backs of the hands and on the proximal parts of the fingers (Figs. 2 and 3). On the inside of the wrist the skin was cracked and red in crevices. The rash had a rough, raised feel, and a branlike exudate could be rubbed off. The rest of the body was free of this skin rash, except a scaly, brownish area, the size of a dollar, over the dorsal surface of the right foot. There was a scaly, dark brown pigmentation and rash about the anus, and the mucous membrane of the rectum was red and angry looking. The rest of the physical examination was negative, except that there was some difference in the muscle strength in the extremities, the left arm and leg being stronger than the right.

The urine findings were negative except for a trace of albumin and an occasional narrow hyaline or granular cast. The blood findings showed a fairly high grade secondary anemia, hemoglobin, 65 per cent; red cells, 3,296,000; leukocytes, 6,250. Differential count: polymorphonuclears, 70 per cent.; small mononuclears, 19.5 per cent.; large mononuclears, 7 per cent.; transitionals, 0.5 per cent.; eosinophils, 2.5 per cent.; myelocytes, 0.5 per cent. No nucleated reds were seen, no polychromatophilia, no basophilic stippling, no anisocytosis. The Wassermann test was negative. Blood pressure, 132 systolic, 90 diastolic. Smears from the exudate on the gums and roof of the mouth showed no spirilla of Vincent, but a long bacillus and diplococci.

A diagnosis of pellagra was made and the patient was placed on a liberal meat diet, with beef juice, and daily intravenous injections of fresh made sodium cacodylate, from 2 to 5 grains (from 0.130 to 0.324 gm.) to the dose. She improved steadily but slowly. She was dismissed from Abbott Hospital on May 21, less than two months after her admission, the dermatitis and pigmentation gone, the mucous membranes free from redness and irritation, the

weakness and exhaustion almost gone, and the anemia corrected to a large degree. A letter from her in July reported no recurrence of the rash or other symptoms.

Dr. Joseph Goldberger, of the U. S. Public Health Service, the recognized authority on pellagra in this country, and Dr. John Butler of Minneapolis, examined the patient and confirmed the diagnosis of pellagra.

STUDIES OF ACUTE INTESTINAL OBSTRUCTION

I. DIFFERENT TYPES OF OBSTRUCTION PRODUCED UNDER LOCAL ANESTHESIA *

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Acute intestinal obstruction as presented in our schools and described in textbooks is often treated as a clinical entity in which there is one chain of symptoms and one type of treatment. The various etiologic factors are mentioned, but no variance of symptomatology or treatment to correspond with the diverse pathology is specified. The mortality rates are also usually classified under one general heading despite the dissimilar pathogenicity.

In a like manner, most of the experimental work of the last thirty years has disregarded the different underlying morbid conditions. The endeavor has generally been to find one specific lethal factor. Little notice has been taken of the extent or type of the lesion produced. This treatment of the subject must be fundamentally wrong. If not, how are we to explain the great differences in the physical and mental condition in acute obstruction cases seen clinically?

One patient, with an acute obstruction of six or eight *hours'* duration, appears to be in profound collapse. His face is pale and the expression anxious. The eyes are sunken, the features pinched, and the skin is covered with a cold clammy sweat. The pulse is very rapid and feeble, the temperature is subnormal. The tongue is dry and parched, and the thirst is incessant. Vomiting is profuse and foul smelling, and is preceded by abdominal pain. The blood pressure has fallen to 60 or 70.

Another patient, with an obstruction of three *days'* duration, seems to be in fairly good condition. The temperature, pulse and respiration are practically normal. The patient may complain bitterly of pain and frequent vomiting, but he presents none of the collapse symptoms shown by the former case. The blood pressure is normal or only slightly lowered.

In addition to this marked physical and mental contrast, these cases, when examined in the surgery or at necropsy, reveal vast differences in the underlying pathologic conditions. The former patient has an acute strangulation, the latter a simple obstruction of the bowel lumen.

In reviewing a series of clinical cases, we noted that the severity of the symptoms and the pathology of the tissues involved usually ran

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parallel, and we believe, therefore, that, clinically, acute obstruction should be divided into two classes: 1. Acute strangulation, those in which there is an interference with the venous, arterial and lymphatic circulation in the bowel wall and mesentery as well as complete obstruction of the intestine lumen. Under this heading can be grouped volvulus, strangulated hernia, intussusception, etc. Clinically, they present pictures similar to the first case described above. This group totals about 80 per cent. of obstruction cases. 2. Acute simple obstruction, those in which there is a complete blockage of the bowel lumen only, with practically no circulatory involvement. The obstruction here may be produced by gallstones, enteroliths, foreign bodies, adhesions or bands. The clinical picture corresponds to the second case described. This group comprises approximately 20 per cent. of the total.

These two classes have a different mortality rate; the process progresses more rapidly to a fatal outcome in one type than in the other, and it seems logical to conclude, therefore, that the cause of death must vary in the two types. As a natural corollary to this, the treatment should be altered accordingly.

The purpose of the following experiments was to ascertain whether this classification would hold true on experimentally produced obstruction, and also to determine whether the lethal factors varied in the different types.

A review of the work on experimental obstruction reveals that few investigators had observed such a distinction although it had been long recognized clinically. Furthermore, no worker has been able to obtain a true postoperative picture of either type. In these investigations, practically all of which were made on dogs, symptoms of ileus comparable to those seen in human beings were not observed. A critical examination of their methods discloses the fact that all operations were performed under ether or ether-morphin anesthesia. These drugs are known to cause a general central depression and an atonic state of the intestinal musculature for from twenty-four to forty-eight hours. It is during this time that all obstruction cases show their most characteristic objective signs. In many strangulation cases, the subjects die within the first eight to forty hours. It seems evident, therefore, that the anesthesia masks the picture.

The first problem was to devise a technic by which we could produce experimentally an obstruction that would leave the animal operated on as nearly normal as possible. All drugs acting on the intestine or with prolonged effect on the central nervous system had to be eliminated. After considerable experimental work, it was found that excellent results could be obtained with local anesthesia by subcutaneous injection of procain and epinephrin, along the expected line of incision one half hour before operation. During the operation, a large amount of the injected

solution seeps out of the tissues into the field of operation and is wiped away. The small fraction remaining in the tissues is very slowly absorbed owing to the vasoconstrictor action of epinephrin. It is rapidly oxidized in the body tissues, and therefore produces slight if any central effect. Within an hour after the injection, there is thus no complicating factor that would not be found in human obstruction cases except the small incision through the linea alba. Dogs, when operated on by this method, present a symptom complex comparable in detail, within the limits of any animal experimentation, to those exhibited by man.

METHODS AND TECHNIC

Dogs were used exclusively in the experimental work. Observations for normal data were made on all dogs for several days previous to operation. All experiments were performed under local anesthesia by careful aseptic methods. About from 40 to 60 c.c. of procain, 0.25 to 0.50 per cent. and epinephrin 1 : 10,000 was injected about one half hour before operation. No toxic symptoms were ever manifested. The animals were strapped on a well padded operating table and were made as comfortable as possible. The surgical procedure was accomplished quickly, seldom consuming more than fifteen minutes, and with little or no trauma. All obstructions were produced by tying the intestine with a heavy cord or small rubber catheter or by clamping with aluminum clamps. Blood pressure was taken under local anesthesia on the femoral artery to avoid the complications with the vagus and sympathetic trunks which occur when the common carotid is used. A standard mercury manometer was used and tracings were recorded on a drum kymograph.

Group 1.—Acute simple obstruction: To demonstrate the typical symptoms of a dog with acute simple obstruction produced under local anesthesia. In this series of twenty-one animals, simple ligation was performed at the duodenojejunal junction on nine animals, the lower jejunal on seven and the upper ileac on five. The symptoms presented at these different tie levels are practically identical. The following protocol of a dog under continuous observation presents the typical picture:

Adult male, black and white mongrel, weight 16 pounds (7.2 kg.), operated on, Jan. 10, 1923; time of operation fifteen minutes, off table at 5:15 p. m.

January 10, 4:00 p. m.: Temperature 102.2 F., pulse 90, respiration 18, blood pressure 150 (systolic).

4:30: Operation; dog active, appears normal in every respect.

5:30: Vomits large amounts of bile stained partly digested food.

6:15: Has been very restless, gets up and lies down frequently and whines.

6:30: Drinks considerable water.

6:45: Drinks again, restless, whines some.

6:50: Retches ten times and vomits 50 c.c. of bile stained alkaline liquid containing some bile content. Yelping precedes this retching.

6:55: Retches severely and vomits.

7:05: Drinks small amount of water several times.
7:20: Restless, head down, appears nauseated.
7:35: Restless, retches, no vomitus.
7:40: Respiration 20, pulse 100, temperature 102.4 F., blood pressure 155.
7:55: Whines loud and long, drinks.
8:00: Resting, occasional subdued whine.
8:15: Dog up, whines loudly, vomits profusely three times; vomitus alkaline watery fluid, some mucus.
8:18: Drinks again, is hypersensitive and apprehensive, lies down.
8:25: Up whining, appears slightly exhausted.
8:55: Has been resting rather quietly.
9:00: Up, drinks, in a minute whining. Vomits three times, lies down.
9:23: Up, whines, retches; no vomitus.
9:30: Drinks small amounts several times.
9:35: Up howling, retches, vomits repeatedly.
9:40: Resting quietly. Temperature 102.8 F., pulse 95, respiration 20, blood pressure 155 (systolic).
9:55: Howls, retches and vomits profusely.
10:00: Resting.
10:10: Up, vomits several times small amounts with some mucus.
10:20: Resting.

From 11:00 p. m. the dog was placed in a cage and was not observed until 7:00 a. m.

January 11, 7:00 a. m.: Dog looks somewhat haggard but is not toxic. Temperature 103.1 F., pulse 95, respiration 18, blood pressure 145.

From 7:00 a. m. to 1:00 p. m., the dog drank often; vomits much less frequent but greater amounts.

4:00 p. m.: Temperature 102.6 F., pulse 90, respiration 18, blood pressure 145. The animal seems in no pain and does not vomit unless he drinks water.

January 12, 2:00 p. m.: Dog appears to be in very good condition. Temperature 102.8 F., pulse 100, respiration 22, blood pressure 145 (systolic). The total vomitus today is 180 c.c. more than the fluid intake. Vomitus is yellowish brown watery liquid, alkaline in reaction and has a slightly foul odor.

January 13, 4:00 p. m.: Temperature 103.0 F., pulse 100, respiration 22, blood pressure 140, vomitus 80 c.c. The animal appears weaker, weight 14.1 pounds (6.4 kg.). Apparently in no pain and has vomited only a few times today.

January 14, 10:10 a. m.: The dog was given a barium sulphate meal. Fluoroscopic examination reveals that the bowel above the tie is still very active. Frequent peristaltic waves are seen starting in the stomach and rapidly running down to the tie at the lower end of the duodenum. The duodenum which is now considerably dilated gradually fills and violent peristalsis continues for several minutes. These waves are followed by a period of quiescence. After a few minutes, a contraction and shortening of the entire duodenum, beginning about a half inch above the tie and quickly extending upward, forces all of the barium sulphate back into the stomach. The duodenum then remains empty for several minutes, after which the above mentioned cycle is again repeated.

4:00 p. m.: Temperature 103 F., pulse 100, respiration 22, blood pressure 140 (systolic). The barium sulphate meal has been regurgitated as well as about 40 c.c. of bile stained fluid.

January 14, 1:00 p. m.: No vomiting today. The tie has evidently cut through and the bowel reunited. Eats ravenously and drinks a great deal. Temperature 102.6 F., pulse 95, respiration 20, blood pressure 145 (systolic).

January 15: No vomitus. Dog has had normal stool. Recovery complete and uneventful.

Of this series, five dogs died of peritonitis following perforation at the base of the tie. In the remaining sixteen dogs, the tie cut through in from three to six days as shown by discontinuance of vomiting and passage of stool, or evidenced by fluoroscopic examination. The only objective symptom displaying any particular variation was the degree of whining that was manifest. This is purely an individual characteristic of the different types used.

TABLE 1.—*Daily Observations on Temperature, Pulse, Respirations and Blood Pressure on Dogs with Simple Obstruction with Recovery*

Dog	Weight, Pounds	Days	Average Daily			Blood Pressure (Systolic)
			Temperature	Pulse	Respiration	
2	43	1	102.4	90	18	150
		2	102.4	110	20	145
		3	102.8	104	20	140
		4	102.8	100	20	155
4	37.1	1	101.8	94	18	152
		2	102.6	100	20	145
		3	102.8	106	18	142
5	11	1	103.4	95	20	148
		2	103.8	110	20	144
		3	104.2	108	20	135
9	20	1	101.6	86	18	156
		2	102.8	88	18	140
		3	102.2	94	20	138
		4	102.3	90	16	144
10	29	1	102.2	84	16	138
		2	102.8	98	18	135
		3	103.6	106	20	138
11	15	1	102.4	86	20	160
		2	102.4	98	22	154
		3	102.6	100	20	148
		4	103.2	104	20	...
15	35	1	102.7	90	16	126
		2	101.9	100	18	120
		3	103.6	104	20	130
16	31	1	102.8	88	20	144
		2	102.9	110	24	148
		3	103.1	106	22	135

This characteristic protocol and the data presented in Table 1 demonstrate that dogs with acute simple obstruction never show any symptoms of collapse although they are noticeably distressed by the violent abdominal pain and profuse vomiting. The pulse and respirations are but slightly increased; the temperature is usually normal, and the blood pressure exhibits but slight variation even after from forty-eight to ninety-six hours. The slight increase in temperature and pulse rate is probably due to the small localized peritonitis which occurs at the point of the tie and the tissue absorption from the abdominal incision. a condition often observed in control animals with an uncomplicated abdominal incision.

The seven unselected cases of acute simple obstruction due to adhesive bands, presented in Table 2, were seen by us at Emanuel Hospital during 1921. All diagnoses were verified at operation. Six patients recovered. One died following resection and end to end anastomosis and a complicating peritonitis.

TABLE 2.—*Human Series of Acute Simple Obstruction Produced by Adhesion Bands* *

Patient	Age, Years	Days	On Day of Entrance: Temperature	Pulse	Respiration	Blood Pressure: Systolic	Diastolic	Results
Mrs. B. E.	28	1	97	80	18	116	82	Recovered
Mrs. E. D. B..	43	7	99.3	90	20	140	92	Died after 9 days
Mrs. F. J.	57	3	99.8	70	18	...	..	Recovered
Mrs. A. F.	38	3	102.4	120	22	130	90	Recovered
Mrs. F. F.	43	3	100.2	94	18	160	90	Recovered
Mrs. S. C. B..	71	3½	99.5	86	22	...	..	Recovered
Mr. L.	56	8	98.6	78	18	150	70	Recovered

* All but one patient made uneventful recoveries after severance of the tissue band.

The subjoined case history demonstrates the striking similarity between clinical and experimental obstruction under local anesthesia.

REPORT OF CASE

History.—Mrs. E. D. B., aged 43, a Christian scientist, stated that the onset of her present illness began one week before entrance by a sudden attack of extremely severe colicky pain localized in the umbilical plane. The pain appeared to come in waves, increasing in severity until a climax was reached followed by a period of quiescence. She soon became nauseated and later began to vomit. Vomiting continued about every thirty minutes, with differing degrees of severity, for the next six days. The evening of entrance the condition had become more severe. At first, the vomitus was food recently eaten, followed by bile tinged liquid. On the second and third days, it was foul smelling. About three hours after the onset, the patient had had bowel movement, but there had been none since then. The temperature had been normal throughout the course. She had had no chills but complained of some cold sweating. From the first, she had been extremely bloated.

The appendix and right ovary had been removed twenty years before. The menstrual history was negative except for three questionable miscarriages. For the last year, she had complained of pain and gas distress after meals.

Physical Examination.—The patient was a normal, well nourished individual. The pathologic condition was confined to the abdomen, which was markedly distended and tympanitic. There was little or no rigidity, but it was tender, particularly over the lower duodenum area, where a palpable mass could be outlined. Auscultation revealed violent borborygmus above the umbilical line.

Laboratory Findings.—Leukocyte count rose from 10,750 at 5 p. m. to 21,200 at 9 p. m., just before operation; differential: polymorphonuclears, 67 per cent.; small mononuclears, 12 per cent.; large mononuclears, 16 per cent.; transitionals, 3 per cent.; eosinophils, 2 per cent. Examination of the urine revealed: specific gravity 1.035; albumin, plus. The blood pressure was 140 systolic, 92 diastolic.

Pathologic Findings.—An adhesion band completely obstructed the lower ileum with recent perforation at the base of the band. There was dilatation above the obstruction, but little or no circulatory involvement.

The foregoing clinical case clearly reveals, as do the experimental ones, that, in simple obstruction, there is but slight deviation from the normal in temperature, pulse, respiration or blood pressure. Furthermore, the symptoms are very similar, and if the obstruction is removed by cutting through or by surgical intervention, most of these patients recover. The low mortality rate is also undoubtedly due, in part at least, to the replacement of body fluids and salts by the introduction of large quantities of physiologic sodium chlorid solution and glucose after operation. The case cited in detail above, in which operation was refused until the eighth day, shows clearly that toxemia if present in these cases, plays but a very small rôle. Of course, if the integrity of the bowel is destroyed by perforation, we are dealing with a complication of a very different nature.

Group 2.—Acute strangulation: To illustrate the symptomatology in dogs with experimentally produced acute strangulation of varying lengths of small intestine. This series includes twelve dogs. As the results are uniform, only one typical protocol will be given in detail. A more comprehensive report on this series will appear later.

Dog 28, healthy Spitz female, weight 17 pounds (7.7 kg.); 9 a. m. normal; temperature 102.2 F., pulse 84, respiration 18, blood pressure 150 (systolic); operated on at 10:20 a. m., off table at 10:35 a. m..

10:20: A complete venous and lymphatic obstruction of a large segment of bowel was produced by twisting and tying off the intestine and mesentery with a small rubber catheter. The tie was not made sufficiently tight to shut off the arterial flow immediately but caused a marked venous occlusion at once.

10:35: Off table, walks around room, appears perfectly normal.

10:47: Vomits 30 c.c. of whitish stomach content, acid to litmus. Whines repeatedly and appears very nervous. Drinks small amount of water.

11:10: After whining and retching, vomits 40 c.c. of alkaline slightly bloody and bile stained fluid.

11:12: Retches and vomits a few cubic centimeters of very thick slimy mucus. Whines repeatedly.

11:19: After severe howling and retching, vomits 20 c.c. of blood stained alkaline fluid. This fluid has evidently come from the obstruction level.

11:26: Howls and retches, but raises no vomitus.

11:38: Howls loudly and vomits 20 c.c. of the usual thick frothy mucus. This fluid has the appearance of egg albumin although it does not give a reaction for albumin.. It is negative for bile and shows but a slight trace of proteolytic and lipolytic enzymes.

11:50: Drinks again.

12:00 m.: Animal is now beginning to show definite collapse symptoms. The eyes are retracted, pupils dilated, ears and tail drooping, nose dry, thirst incessant and the extremities cold. The respirations are loud and rapid, the pulse is greatly augmented and of small volume. The gait is unsteady and animal leans heavily against the side of the cage. The entire attitude is one of extreme dejection.

12:00 m. to 1:00 p. m.: Frequent drinking and vomiting during this hour. The dog is rapidly becoming more dazed and whines less frequently. Collapse is more pronounced.

1:10: Whining at short intervals, drinks frequently. Temperature 101.5 F., pulse 135, respiration 38, blood pressure 80 (systolic). This doubling of the

pulse and respiratory rates, subnormal temperature and extreme fall in blood pressure indicates an already advanced case of shock.

1:40: Retches profusely, then vomits 140 c.c. clear slimy mucus.

1:45: Drinks considerable and whines. Very weak. Gait staggering, falls when attempt is made to lie down.

1:56: Gets up with effort, cries, vomits 25 c.c. mucus. Drinks again.

1:59: Lies down, retches but raises no vomitus.

2:03: Whines, gets up, drinks and lies down again.

2:28: Gets up, howls, retches and vomits 50 c.c. of clear mucus.

2:45: Dog resting, breathing very heavily. Whines frequently.

2:55: Temperature 100.8 F., pulse 140, respiration 40, blood pressure 70.

3:02: Whines, drinks, retches violently and vomits 50 c.c.

3:17: Resting quietly, suddenly up, whining, drinks and then yelps.

3:40: Retches twelve times, and finally raises 20 c.c. of slimy mucus.

3:55: Yelps frequently and drinks; exhaustion more marked.

4:11: Retches fourteen times, vomits a few cubic centimeters.

4:25: Drinks small amount, whines, retches but raises no vomitus.

4:47: Drinks again, two minutes later retches twenty-two times and then vomits 60 c.c. Temperature, 100.2 F.; pulse, 240; respiration, 44; blood pressure, 60. The pulse has shown a profound increase and is of small volume. The respiration has trebled its rate, and the rectal temperature is subnormal. The blood pressure is very low.

5:30: There has been a vomitus of 175 c.c. more and 125 c.c. of water has been consumed since the last period. Whining is less frequent and greatly subdued.

8:00: Consumed 140 c.c. of water; about 160 c.c. of vomitus since 5:30. Temperature, 99.2 F.; pulse, 300; respiration, 63; blood pressure, 62. The animal was hardly able to stand and was insensitive to most pain. The belly was opened without a local anesthetic and the belly cavity and bowel examined. The gangrenous loop was immensely distended and black. There was no evidence of perforation. The segment was perforated with a needle, and a stream of bloody fluid ejected in a fine stream for 3 feet. No evidence of pain throughout this procedure.

8:45: Dog up, drinks, and then falls down.

9:00: Resting in cage. Retches suddenly and vomits a few cubic centimeters.

9:15: Prone in cage. Temperature, 102; Pulse, 300; respiration, 76; blood pressure, 40.

10:00: Moribund; necropsy.

All dogs in the series died in from seven to twenty-four hours. In all cases, the blood pressure exhibited a conspicuous fall within six hours after the strangulation was produced. Within two hours, there was always at least a doubling of the pulse rate. A consistent increase in respiratory rate and usually a fall in temperature were noted within the first from eight to ten hours.

These experiments represent strangulation of from 15 to 35 inches (37.5 to 87.5 cm.) of small intestine, the ligature being tied in such a manner as to cause immediate and complete venous stasis. These two factors, namely, the length of the segment and the completeness of venous obstruction, are extremely important, as they determine directly the degree and rapidity of onset of shock. In cases in which the segments are long and there is complete venous occlusion, shock appears early and is profound. When short loops are employed, it comes on slowly and is seldom very marked. There are naturally all gradations between

these two extremes. It is thus evident that, in acute strangulation, the lethal factors vary in all cases. The extent of shock is directly proportionate to the length of intestine involved and the degree of venous obstruction.

The foregoing experimental group is comparable only to the most severe human cases of volvulus and extensive internal strangulation. The majority of cases seen clinically are inguinal and femoral hernia, with but a few inches of strangulated intestine and only partial venous obstruction. Furthermore, the patients are usually seen within a few hours from onset, and early surgical intervention occurs before alarming symptoms can develop. For these reasons, we were unable to obtain a sufficiently large series of clinical cases similar to our experimental type. A review of the case reports in the literature will convince one of the striking similarity between symptomatology of the experimental cases and that of the human cases.

Following is a protocol presenting the symptomatology of a dog with simple obstruction, under morphin and local anesthesia (procain), demonstrating the effect of morphin on the objective signs.

Male mongrel, weight 17 pounds (7.7 kg.), operated on Jan. 10, 1923, at 3:30 p. m., with morphin, 1 grain.

A simple obstruction was produced by ligating the duodenum with a heavy cord. A rather large window of cellusilk was sewed into the abdominal wall after the removal of part of the recti. The bowel could be observed directly at any time on the table.

4:00: Sleeping quietly.

4:30: Peristalsis can now be elicited on pinching the bowel, but there are no cramp spasms or violent waves evident.

5:00: Resting quietly.

6:40: Very shallow peristaltic waves can be seen for the first time passing over about 8 cm. of intestine above the tie. Dog whines while this occurs.

7:00: Whines occasionally.

7:30: More or less repeated peristalsis, rather rapid, can now be seen running over the visible segment of bowel. The waves stop a centimeter or two above the obstruction. Occasional whimper during activity of the waves.

8:30: Almost continuous peristalsis, quite vigorous, is present over the visible segment. The waves follow each other at intervals of about from two to four seconds. Repeated antiperistalsis can now be seen beginning above the obstruction and passing over the entire segment. These waves are not preceded by the true inhibitory phase but appear more as a massive contraction originating just above the obstruction.

8:40: Dog awake. Tries to get up.

9:00: Bowel is more active.

9:10: Dog whines, struggles to get up; segment above tie is in spasm.

9:30 to 11:00: Occasional whines. Dog has not vomited while under observation.

11:00 p. m. to 9:00 a. m.: Placed in cage and not observed. Peristalsis now present above and below tie. Animal in good condition; killed for tissue examination.

These observations clearly demonstrate that morphin inhibits peristalsis for a period of from three to six hours and thus prevents the appearance of the usual symptom complex. If it is used in conjunction with ether, the effects are still more prolonged.

COMMENT

So far as we were able to ascertain, no previous work of this nature has ever been attempted under local anesthesia. The method has its difficulties, requires patience and necessitates minimum manipulation. However, these very factors render the experimental states as nearly as possible like those that occur under normal conditions. Further, we have been able to reproduce, in these experimental animals, symptom complexes which simulate and parallel the clinical entities. It seems logical, therefore, that the results and deductions in a large measure should be applicable to human cases.

The division of acute intestinal obstruction into acute simple obstruction and acute strangulation appears to be amply proved by this experimental work. In the former, we are dealing with obstruction of the lumen of the intestine without circulatory involvement of much consequence. In the latter, there is segmental obstruction plus extensive vascular derangement.

The rapid fall in blood pressure, the great increase in pulse and respiratory rates, the subnormal temperature and the certain speedy death in acute strangulation when compared with the normal temperature, pulse, respiration and blood pressure in acute simple obstruction indicate that the underlying lethal factors must be different in each type.

In acute strangulation, we are dealing primarily with a shock complex, in which toxemia, dehydration and chlorid loss play but little part. In simple obstruction, shock is not present, and toxemia per se is but a slight factor, if present at all, death instead being due to perforation and peritonitis or, in uncomplicated cases, to inanition, dehydration and chlorid deficiency. These differences in pathology and mortality demand special operative and postsurgical treatment for each type.

CONCLUSIONS

1. Intestinal obstruction as produced experimentally under local anesthesia in dogs closely resembles the human symptom complexes.

2. Experimental acute intestinal obstruction can be classed under two general headings, (1) acute simple obstruction and (2) acute strangulation.

3. The pathology of these two groups is distinctly separable and the lethal factors are different.

4. The symptom complexes of the two types are also very different. Acute simple obstruction shows relatively slight variations in temperature, pulse, respiration and blood pressure; while acute strangulation causes profound changes in these physiologic indicators.

5. Uncomplicated blood pressure observations on dogs following bowel obstruction, can be secured from the femoral artery under local anesthesia.

6. Ether and morphin must be eliminated in experimental studies of the acute symptomatology of intestinal obstruction.

THE QUANTITATIVE AMOUNT OF LIPOID MATERIAL IN THE KIDNEY AND ITS RELATION TO THE FUNCTIONAL RESPONSE IN EXPERIMENTAL NEPHRITIS*

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The presence of various forms of fatty materials, i. e., lipoids, in the kidney in acute nephritis is one of the most important histologic findings. The relation of these substances to the altered functions of the kidney and to the latter stages of chronic nephritis is not well known. An understanding of these relations would serve as stepping stones toward the solution of many problems which are of vital clinical importance.

An experimental study of lipoid changes in nephritis in animals offers an approach which at present is not possible in dealing with early nephritis in man. It is only in exceptional instances that gross material can be obtained from a patient with early nephritis, since he either recovers or progresses on to a chronic condition.

In producing kidney changes we have used uranium nitrate because the histology of this type of experimental nephritis has received a great amount of study and is well understood.[1] Uranium nitrate has a particular action on renal epithelium, and the degree of nephritis it produces may be controlled by the dosage. The resulting nephritis simulates early nephritis in man.

Lipoid material in the kidney may be studied in two ways: (1) microscopically by the use of special stains; (2) chemically by means of quantitative extraction. MacNider,[2] using the first method, studied the amount and distribution of stainable lipoid material in the renal epithelium of dogs, and demonstrated microscopically the degree of fatty changes. In addition to the first method, we have used the second and have recorded the percentage of fatty change in the kidney and

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1. MacNider, W. de B.: A Functional and Pathological Study of Chronic Nephropathy Induced in the Dog by Uranium Nitrate, J. Exper. Med. **29**:513 (May) 1919.

2. MacNider, W. de B.: A Preliminary Paper on the Relation Between the Amount of Stainable Lipoid Material in the Renal Epithelium and the Susceptibility of the Kidney to the Toxic Effect of the General Anesthetics, J. Pharmacol. & Exper. Therap. **17**:289 (May) 1921.

liver. We have attempted to correlate the functional response of the kidney with the actual amount of lipoid material and with the histologic pictures.

We have also contrasted the extent of the fatty change in the kidney and liver, and have endeavored to determine in which organ these changes occur first.

Material.—Young rabbits, each weighing about 4 pounds (1,814 gm.) were used.

Method.—The rabbits were divided into five groups.

Group 1.—Seven control animals were in this group.

Group 2.—The rabbits in this group were given 4 mg. of uranium nitrate subcutaneously and then killed at progressively increasing intervals, twelve, eighteen, twenty-four, forty-eight, seventy-two and ninety-six hours from the time of inoculation.

Group 3.—The procedure in this group was the same as that outlined for Group 2, excepting that the experiment was followed through to the fifteenth day.

Group 4.—These rabbits were given 4 mg. of uranium nitrate subcutaneously, and immediately after the injection were given 25 c.c. of 3 per cent. sodium carbonate solution intravenously. They were then killed at the stated hours following the injection.

Group 5.—Seven rabbits were given four weekly doses of uranium nitrate. They were then allowed to rest for two weeks. In this manner a well marked subacute nephritis was produced. At the end of six weeks they were treated as the rabbits in Group 1.

The kidney function of each animal was studied by means of a phthalein test, by a chemical and microscopic examination of the urine and by a determination of the nonprotein nitrogen, the urea nitrogen and the carbon dioxid of the blood. These tests were repeated just before each animal was killed. Then portions of the kidneys and of the liver were extracted with ether. The technic of this method was as follows. A kidney was taken from the animal immediately after its death and weighed. It was chopped up finely and ground in a mortar with gypsum. The ground tissue, together with the gypsum, was put into an extracting thimble, the thimble placed in a Soxhlet apparatus and covered with a liberal quantity of anhydrous ether. Extraction was then carried on over an electric plate for ten hours. Following this, the excess of ether was evaporated from the flask containing the extracted fat and the flask placed in a drying chamber for twenty-four hours. The flask was then weighed carefully, and the exact amount of lipoid material ascertained by subtracting the weight of the empty flask from the weight of the flask when it contained

the lipoid. The amount of lipoid was recorded as the percentage of the total weight of the organ. Two separate determinations were made from each kidney and liver and an average of the two readings recorded.

Frozen sections of the kidney and liver were made and stained for fat, using Herxheimer's [3] technic. Other sections, cut in paraffin, were stained with hematoxylin and eosin.

The nonprotein nitrogen and the urea nitrogen were determined by the methods of Folin and Wu.[4] The carbon dioxid was determined by the method of Van Slyke.[5] It is stated as the capacity of the blood serum for CO_2. In making the phthalein determinations, each rabbit was given 75 c.c. of water by stomach tube. One cubic centimeter of the dye was then injected subcutaneously. The readings were made two hours after the urine in the bladder had been expressed by massage.

Tables 1, 2, 3, 4 and 5 give the data obtained from the corresponding groups of animals.

TABLE 1.—*Control Animals in Group 1*

Animal	CO_2, Percentage by Volume	Nonprotein Nitrogen, Mg.	Uranium Nitrate, Mg.	Phthalein Percentage	Urine	Percentage of Lipoid	
						In Kidney	In Liver
1	65	38.4	20.7	75	Negative	3.63	3.04
2	50	44.2	27.0	68	Negative	3.65	3.46
3	55	36.2	22.0	64	Negative	3.10	3.18
4	68	52.4	32.2	78	Negative	3.19	3.10
5	54	48.0	28.7	56	Negative	3.40	3.80
6	52	34.0	16.4	58	Negative	3.60	3.80
Average						3.43	3.42

RESULTS

The phthalein output in a series of seven control animals, and in the twenty-eight animals at the beginning of the experiments varied from 46 to 85 per cent. The carbon dioxid of the blood serum ranged from 52 to 71 per cent. by volume. The nonprotein nitrogen of the blood varied from 36 to 65 mg. per hundred cubic centimeters of blood. The urea nitrogen ranged from 16 to 30 mg. per hundred cubic centimeters. The urine did not contain pathologic constituents either on chemical or microscopic examination.

Stainable lipoid was not found in frozen sections of the kidneys of the control animals. The liver, however, contained fine droplets in the cells throughout the liver lobule.

3. Method given by MacNider in Footnote 2, page 292.

4. Folin, O., and Wu, H.: A System of Blood Analysis, J. Biol. Chem. **38**:81 (May) 1919.

5. Van Slyke, D. D., and Cullen, G. E.: The Bicarbonate Concentration of the Blood Plasma; Its Significance, and Its Determination as a Measure for Acidosis, J. Biol. Chem. **30**:289 (June) 1917.

Twenty-four hours following an injection of 4 mg. of uranium nitrate into an animal, five droplets of lipoid were found in the kidney, in the cells lining the loops of Henle and the proximal convoluted tubules. Fine droplets were present in the cells throughout the liver lobule, in an amount considerably in excess of the controls.

The kidneys from an animal killed forty-eight hours following a uranium nitrate intoxication, contained large droplets of lipoid in the cells lining the loops of Henle, while the cells lining both the proximal and distal convoluted tubules contained fine lipoid droplets which made them stand out sharply. These droplets occurred throughout the cell in contrast to the peripheral location of the droplets in the animal in which the intoxication was of twenty-four hours standing. The liver cells contained an increased number of small lipoid droplets, especially about the periphery of the lobule.

At the end of seventy-two hours, ninety-six hours and one hundred and twenty hours, both fine and large droplets of lipoid were present in the kidney and liver, in the areas indicated, but apparently in decreased and varying amounts. This may have been due in part to other microscopic evidences of injury becoming more pronounced. These microscopic variations led us to extract the lipoid material from these tissues by chemical methods, in order to determine the exact percentage of lipoid material present at the various periods.

The lipoid material in the kidneys of seven control animals varied from 3.10 to 3.66 per cent., with an average of 3.43 per cent. The percentage of lipoid in the livers of these animals varied from 3.04 to 3.80, with an average of 3.42 per cent.

In Table 2 it will be noted that twelve hours following an injection of 4 mg. of uranium nitrate into a normal animal, a marked drop in the carbon dioxid of the blood serum resulted. This evidence of acidosis occurred with regularity. At this time there was no appreciable change in the nonprotein nitrogen and urea nitrogen of the blood. The urine showed a faint trace of albumin, but acetone, diacetic acid and reducing substances were absent. The phthalein output was not altered. The amount of lipoid material extracted from the kidney was 3.33 per cent. of its total weight, and from the liver, 3.89 per cent. These figures are little changed from the average normal readings of 3.43 per cent. and 3.42 per cent. for the kidney and liver respectively.

Eighteen hours following the injection of a similar amount of uranium nitrate into the second animal of the series, an appreciable rise in the nonprotein nitrogen and urea nitrogen of the blood occurred. The carbon dioxid of the blood serum had fallen from 66.1 to 40.4 per cent. by volume. The phthalein output was reduced from 54 per cent. to 45 per cent. in two hours. The urine had a heavy trace of albumin with an occasional hyaline cast. The lipoid material of the

kidney and of the liver had increased to 3.56 per cent. and 5.41 per cent., respectively.

Twenty-four hours following the uranium injection into animal number 3 of the series, the nonprotein nitrogen and urea nitrogen were increased to 78 and 48 mg., respectively. The carbon dioxid of the blood fell from 63.4 to 40 per cent. by volume. The two hour phthalein was reduced from 65 to 35 per cent. and the urine contained albumin, hyaline casts and a trace of acetone. The total lipoid of the kidney had increased to 3.78 per cent. The total lipoid of the liver was 3.85 per cent.

TABLE 2.—*Normal Animals in Group 2*

Animal	Amount Uranium Nitrate, Mg.	CO_2, Percentage by Volume	Nonprotein Nitrogen, Mg.	Uranium Nitrate, Mg.	Phthalein, Percentage	Urine	Percentage Lipoid: In Kidney	Percentage Lipoid: In Liver
1. Normal	...	57.6	45.6	18.9	80	Negative	....	....
12 hr. fol. Uran.	4	31.8	46.5	26.1	85	Albumin, faint trace	3.33	3.80
2. Normal	...	66.1	58.0	25.6	54	Negative	....	....
18 hr. fol. Uran.	4	40.0	65.2	30.2	45	Albumin, faint trace	3.56	5.41
3. Normal	...	63.4	50.4	15.0	65	Negative	....	....
24 hr. fol. Uran.	4	40.4	78.0	48.0	35	Albumin, casts, trace acetone	3.78	3.85
4. Normal	...	59.5	50.0	24.0	45	Negative	....	....
48 hr. fol. Uran.	4	39.0	171.4	72.0	..	Albumin, casts, acetone, diacetic acid	3.17	3.66
5. Normal	...	60.4	65.4	28.3	65	Negative	....	....
72 hr. fol. Uran.	4	44.8	250.0	111.0	..	Albumin, casts, acetone, diacetic acid, reducing sub.	2.23	3.48
6. Normal	...	59.5	60.0	27.2	58	Negative	....	....
96 hr. fol. Uran.	4	38.5	68.2	31.7	19	Albumin, casts, acetone, diacetic acid, reducing sub.	2.48	3.46

Forty-eight hours following the uranium injection into animal number 4, the carbon dioxid was reduced from 59.5 to 39 per cent. by volume. The nonprotein nitrogen had increased from 50.4 to 171.4 mg. and the urea nitrogen from 24 to 72 mg. The final phthalein determination in this instance was not made. The lipoid material in both the kidney and the liver was decreased to 3.17 per cent. and 3.66 per cent., respectively.

The carbon dioxid of the blood in animal number 5 that was killed seventy-two hours following the intoxication, had decreased from 60.4 to 44.8 per cent. by volume. The nonprotein nitrogen and the urea nitrogen of the blood had increased from 65.4 and 28.4 to 250 and 111 mg. per hundred cubic centimeters of blood. The phthalein was lost but the urine contained albumin, hyaline and granular casts, acetone

and diacetic acid and a reducing substance. The total lipoid material of the kidney was decreased to 2.23 per cent. and of the liver to 3.48 per cent.

Animal number 6 of the series, killed ninety-six hours following its intoxication had a decrease in the carbon dioxid of the blood serum from 59.3 to 38.5 per cent. by volume. The nonprotein nitrogen and the urea nitrogen at the outset were 60 and 27.2 mg. and had changed to 68.2 and 31.7 mg. per hundred cubic centimeters of blood. The

TABLE 3.—*Normal Animals of Group 3*

Animal	Amount Uranium Nitrate, Mg.	CO_2, Percentage by Volume	Nonprotein Nitrogen, Mg.	Uranium Nitrate, Mg.	Phthalein, Percentage	Urine	Percentage Lipoid In Kidney	Percentage Lipoid In Liver
1. Normal	...	60.0	58.8	30.0	60	Negative	....	....
6 hr. fol. Uran.	4	49.9	53.0	29.0	65	Negative	4.2	3.22
2. Normal	...	70.0	51.0	24.0	52	Negative	....	....
12 hr. fol. Uran.	4	55.0	57.5	22.4	40	Albumin, faint trace	4.22	....
3. Normal	...	64.4	58.8	33.0	60	Negative	....	....
18 hr. for. Uran.	4	40.0	57.6	34.0	20	Albumin, casts	7.3	3.76
4. Normal	...	49.9	49.4	26.6	57	Negative	....	....
24 hr. fol. Uran.	4	32.2	58.8	42.7	30	Albumin, casts	....	4.68
5. Normal	...	52.4	52.8	38.0	70	Negative	....	....
48 hr. fol. Uran.	4	29.0	60.0	41.9	10	Albumin, casts, acetone, diacetic acid, reducing sub.	5.77	2.85
6. Normal	...	53.8	58.2	32.0	54	Negative	....	....
72 hr. fol. Uran.	4	34.5	153.57	128.57	24	Albumin, casts, acetone, diacetic acid	1.36	1.30
7. Normal	...	58.0	60.0	35.7	55	Negative	....	....
168 hr. fol. Uran.	4	17.7	546.0	500.0	40	Albumin, casts, acetone, diacetic acid, reducing sub.	1.805	2.70
8. Normal	...	60.5	44.4	26.7	60	Negative	....	....
360 hr. fol. Uran. (15 days)	4	59.0	46.87	39.47	44	Albumin, trace; few hyaline casts	2.252	2.21

two hour phthalein output had fallen from 58 per cent. to 19 per cent. The urine contained the same abnormal contents as noted in animal number 5. The total lipoid material of the kidney was 2.48 per cent. and of the liver 3.45 per cent.

Series number 3 differed from series number 2 in that the determinations started at six hours following the injection of uranium and were also made on the seventh and fifteen days. By the seventh day the nonprotein nitrogen and the urea nitrogen of the blood were still high, 153 and 128 mg. The carbon dioxid was 17.7 per cent. by volume. The phthalein output was decreased from 55 per cent. to 40 per cent. Albumin and occasional hyaline casts were still present in the urine.

The most interesting findings were the very much decreased amounts of lipoid material. On the seventh day the total lipoid of the kidney was 1.805 per cent. and of the liver 2.70 per cent. On the fifteenth day the lipoid of the kidney was 2.25 per cent. and of the liver 2.21 per cent. These figures were lower than any others that we had obtained.

The data in Table 4 were obtained from animals given 25 c.c. of 3 per cent. sodium carbonate solution at the time of the uranium injection. It will be noted that the urine did not present the marked

TABLE 4.—*Sodium Carbonate Solution Given at Time of Uranium Nitrate Injection to Rabbits in Group 4*

Animal	Amount Uranium Nitrate, Mg.	CO_2, Percentage by Volume	Nonprotein Nitrogen, Mg.	Uranium Nitrate, Mg.	Phthalein, Percentage	Urine	Percentage Lipoid: In Kidney	Percentage Lipoid: In Liver
1. Normal	...	71.0	39.7	18.27	72	Negative	....	....
6 hr. fol. Uran.	4	69.1	42.63	16.79	65	Negative	3.2	3.0
2. Normal	...	48.8	41.1	17.64	60	Negative	....	....
12 hr. fol. Uran.	4	50.3	34.5	25.42	44	Albumin, trace	3.71	7.2
3. Normal	...	66.4	40.2	18.0	58	Negative	....	....
18 hr. fol. Uran.	4	69.3	40.0	23.08	48	Albumin, trace	3.84	3.80
4. Normal	...	58.8	36.6	16.6	64	Negative	....	....
24 hr. fol. Uran.	4	52.0	36.6	20.0	45	Albumin, occas. casts	5.52	4.65
5. Normal	...	59.6	36.32	21.66	68	Negative	....	....
48 hr. fol. Uran.	4	22.6	51.0	27.3	40	Albumin, casts	3.51	4.34
6. Normal	...	52.2	50.4	19.9	62	Negative	....	....
72 hr. fol. Uran.	4	22.3	222.0	167.0	22	Albumin, casts, acetone, diacetic acid	2.44	3.20
7. Normal	...	50.0	54.2	17.9	40	Negative	....	....
96 hr. fol. Uran.	4	35.3	250.0	147.5	18	Albumin, casts, acetone, diacetic acid	2.48	3.67

changes that were observed in Tables 2 and 3. Traces of albumin were present, but acetone and diacetic acid were only found at the seventy-two and ninety-six hour periods. The phthalein output was reduced. The carbon dioxid of the blood was practically unaltered in the six, twelve, eighteen, and twenty-four hour experiments. The increase in the nonprotein nitrogen and urea nitrogen of the blood was also delayed, but marked retention occurred in the animals of the seventy-two and ninety-six hour period. The variation in the total amount of lipoid material followed approximately the same curve as in the former series, but greater variation was obtained. The decrease in the amount of lipoid material at seventy-two and ninety-six hours was marked, and reached 2.44 per cent. and 2.48 per cent. for the kidney and 3.20 per cent. and 3.68 per cent. for the liver.

Table 5 records the findings in a group of animals in which a subacute nephritis had been produced by four weekly injections of uranium. After a two weeks rest, a final injection of 4 mg. of uranium was given, and the experiments concluded twelve hours, eighteen hours, twenty-four hours, etc., later as in the previous series. The urine of these animals contained faint traces of albumin only. Other evidences of pathology such as acetone, diacetic acid and reducing substances were absent. The phthalein excretions of the whole were somewhat reduced ranging from 60 per cent. to 32 per cent. Following the final injection of uranium the phthalein output was again reduced, the lowest

TABLE 5.—*Subacute Nephritis on Which an Acute Nephritis Was Superimposed in Rabbits of Group 5*

Animal	Amount Uranium Nitrate, Mg.	CO_2, Percentage by Volume	Nonprotein Nitrogen, Mg.	Uranium Nitrate, Mg.	Phthalein, Percentage	Urine	Percentage Lipoid In Kidney	Percentage Lipoid In Liver
1. Subacute.....	16	59.5	50.0	25.8	50	Trace albumin	3.03	3.21
2. Subacute.....	20	48.0	58.25	24.7	60	Trace albumin	....	....
12 hr. fol. Uran.....	..	50.0	72.28	37.49	45	.....	2.22	3.55
3. Subacute.....	20	55.7	68.1	41.6	38	Trace albumin	....	....
18 hr. fol. Uran.....	..	58.0	54.5	30.3	42	.....	2.87	3.27
4. Subacute.....	20	53.8	51.6	28.03	32	Albumin	....	....
24 hr. fol. Uran.....	..	59.0	51.7	30.09	67	.....	3.06	3.74
5. Subacute.....	20	57.6	62.5	27.2	45	Albumin	....	....
48 hr. fol. Uran.....	..	49.0	48.04	24.0	35	.....	3.71	4.07
6. Subacute.....	20	57.0	47.2	30.9	48	Albumin	....	....
72 hr. fol. Uran.....	..	51.9	51.2	28.3	33	.....	3.15	3.52
7. Subacute.....	20	56.7	70.8	42.89	38	Albumin	....	....
96 hr. fol. Uran.....	..	54.0	56.07	32.9	25	.....	2.37	3.38

reading being 25 per cent. in the ninety-six hour animal. In this animal the total lipoid material was lower than in the other animals of the series. The nonprotein nitrogen and the urea nitrogen of the blood were slightly increased as a result of the repeated uranium injections, but following the final injection there was very little change and in three instances (the eighteen, forty-eight and ninety-six hour animals), there was a slight decrease in the amount of these substances. This is easily explained. Following repeated injections of uranium an animal develops a tolerance for this intoxication and increasingly larger amounts must be given to produce marked results.[6] Since the final dose in this series was not larger than the former doses that had been given to produce the subacute nephritis, the intoxication incident to the final injection was minimal. The degree of acidosis as determined by the carbon dioxid of the blood serum bears this out. Before the

6. Nuzum, F. R., and Rothschild, L. L.: Experimental Uranium Nephritis, a Chemical and Pathologic Study, Arch. Int. Med. **31**:894 (June) 1923.

final injection the carbon dioxid varied from 48 to 57.6 volumes per cent., whereas the readings following the final injection varied from 49 to 55.7 volumes per cent. The amounts of lipoid material in the kidney and liver presented less variation than in the other experiments. The lipoid in the control animal of this series was practically the same as in normal animals, 3.03 per cent. and 3.21 per cent. for the kidney and liver respectively. In the twelve and eighteen hour animals the amounts of lipoid in the kidney were recorded as 2.22 per cent. and 2.87 per cent., which is considerably lower than the other animals of the series. However, the increase in the twenty-four and forty-eight hour animals and the decrease after the forty-eight hour period followed the curves obtained in the other series. The increase in the lipoid material of the liver reached a maximum of 4.07 per cent. at the forty-eight hour period. This curve follows closely that of the change in the amount of lipoid in the kidney.

COMMENT

Lipoid material in the epithelial cells lining the convoluted tubules and the limbs of Henle of the kidney and the parenchymal cells of the liver lobule is demonstrated with fat stains following uranium intoxication. Whether this material represents an infiltration or is a degeneration of the protoplasm of the individual cell, is a matter that has occasioned much discussion. Fatty degeneration of the cell protoplasm was perhaps best attacked by Rosenfeld.[7] He found that if an animal rendered fat free by starvation, was fed tallow and then poisoned, the fat depots yielded the tallow to the degenerated organs. Whereas, if an animal was rendered fat free by starvation and then poisoned, degeneration could not be demonstrated. Similar observations have been made in starved human beings by Lebedeff.[8] Fischler[9] carried soap solution through excised kidneys and obtained in this way a picture of fat degeneration. Lusk[10] and his pupils observed these infiltrative changes in phosphorus poisoning, and interpreted them as an attempt on the part of injured cells to keep themselves alive.

But in spite of these and similar observations, pathologists have always felt that fatty infiltration does not explain the morphologic cell changes. It has been found that Rosenfeld's observations have notable exceptions, and that the total fat content of a fatty organ is not always

7. Rosenfeld, F.: Gibet es eins fettige Degenerations? Verhandl. d. Kong. f. inn. Med., 1897.

8. Lebedeff: Ueber Fettansatz in Thierkorper, Arch. f. d. ges. Physiol. **31**: 11, 1883.

9. Fischler: Ueber Experimentell erzeugte Fettsynthese, utc., Virchows Arch. f. Path. Anat. **174**:514, 1903.

10. Lusk: Metabolism in Phosphorus Poison, Am. J. Physiol. **19**:109, 1907.

increased but is occasionally actually diminished in weight. Work which has been done on the nature of autolysis has been particularly helpful in deciding that the protoplasm of cells may actually undergo fatty degeneration. Both in autolytic changes, and in the process of parenchymatous degeneration fine granules make their appearance within the cells.[11] These fine dust like particles fuse to form larger droplets and finally the entire cell may be filled. These substances differ in two ways from ordinary neutral fat.[12] Physically, they give double refraction of polarized light. Chemically, their decomposition often results in the formation of glycerin phosphoric acid. Virchow called these substances "myelins." More recent investigations have shown that myelins include such substances as lecithin, protagon and cholesterol.[13] These were termed lipoids by Overton. They occur in animal cells in abundance and their decomposition bodies occur in traces in the urine. These decomposition bodies, on further breaking down may yield neutral fat (Oertel).[14]

Studies of this nature have fairly demonstrated not only that fatty degeneration of cell protoplasm occurs, but that fatty infiltration and fatty degeneration are intricately related and doubtless often occur together, and diminished alkalinity of the blood which occurs in nephritis is an added factor in affecting these degenerative changes.[15]

The presence of lipoid material in the kidneys and liver, following uranium intoxication, may thus be ascribed both to fatty infiltration and degeneration. Whether one process or the other is especially responsible for the presence of lipoid material within the secreting cells of the kidney is of less import than the relation of these substances, when present, to ability of the kidney to function.

We have found that the maximum increase of stainable lipoid, following a uranium intoxication, occurs within twenty-four hours in the kidneys and livers of animals that were previously normal. In animals in which a subacute nephritis had been established by repeated uranium injections, a maximum increase of lipoid in tissue organs occurred in forty-eight hours. After this there is a diminution in the amount of this material, this diminution continuing until the fifteenth day in one of our experiments (Charts 1 to 4).

Both the initial increase and the succeeding decrease in the amount of lipoid material were demonstrated much more satisfactorily by the

11. Waldvogel: Autolyse und fettige Degeneration, Virchows Arch. f. Path. Anat. **175**:1, 1904.

12. Oertel, H.: The Anatomical Histologic Processes of Bright's Disease, Philadelphia, W. B. Saunders Company, 1910, p. 118.

13. Aschoff: Beitr. z. path. Anat. u. z. allg. Path. **47**:7, 1911.

14. Oertel and Mandel: New York University Bull. M. Sc. **1**:165, 1901.

15. Oertel, H.: The Anatomical Histologic Processes of Bright's Disease, Philadelphia, W. B. Saunders Company, 1910, p. 126.

extraction method than by the staining technic. The former gave data which we have plotted as curves, whereas the staining method gave variable results and at best was a matter of estimate.

In MacNider's [16] hands the staining tecnic was more successful than in ours. Using dogs, he demonstrated a microscopic increase in the amount of stainable lipoid as early as six hours after the uranium intoxication. At twelve hours the amount of lipoid material was increased, and at twenty-four hours there was a still greater increase. At the end of forty-eight hours he found little if any change in the amount of lipoid.

The decrease in the amount of lipoid material after the twenty-four to forty-eight hour period is undoubtedly due to retrograde processes

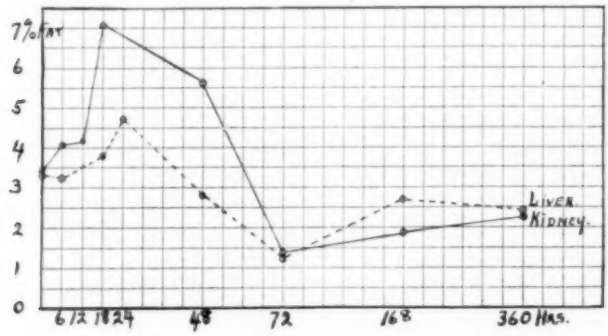

Chart 1.—The percentage of lipoid material in the kidney and liver at stated periods, following the onset of an acute nephritis.

that follow the lipoid change. These processes are evident both in frozen sections stained with scarlet red and in paraffin sections stained with hematoxylin and eosin. The endothelial cells lining the convoluted tubules become so swollen within the forty-eight hour period that they obliterated the lumen of the tubule. By this time vacuolization and necrosis are especially advanced in the endothelial cells of the convoluted tubules. The same degenerative processes are present in the liver, the cells at the periphery of the lobule being affected most severely.

The total amount of extractable lipoid, as determined in our control animals, was practically the same in the kidney, 3.43 per cent., as in the liver, 3.42 per cent. In one series of normal animals (Chart 1), the increase in the lipoid material in the kidney occurred somewhat earlier

16. MacNider, W. de B.: Concerning the Amount and Distribution of Stainable Lipoid Material in Renal Epithelium in Normal and Acutely Nephropathic Animals, with Observations on Functional Responses of the Kidney, Proc. Soc. Exper. Biol. & Med. **19**:222, 1922.

and to a greater degree than in the liver. In the second series of normal animals (Chart 2), in the bicarbonate group (Chart 3) and the subacute nephritis group (Chart 4) the reverse was true. However, in view of the close similarity of the curves depicting these changes, we feel that little significance can be attributed to the somewhat earlier and more marked changes observed in the liver in three of the four groups of animals.

The functional response of the kidney following the uranium intoxications, demonstrates that the lipoid changes occur before the functional response is altered. At the six hour period the functional response is still unaltered whereas a lipoid change is demonstrable in both kidney and liver. At the twelve hour period the lipoid change is very evident, while the phthalein response of the kidney may still be normal and the nonprotein nitrogen and urea nitrogen of the blood remain unaltered.

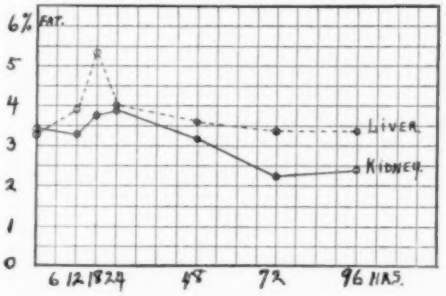

Chart 2.—The per cent. of lipoid material in the kidney and liver in a second group of animals following the onset of an acute nephritis. The per cent. of lipoid in the liver is somewhat increased over that found in the kidney.

At this time, however, there is usually a decrease in the carbon dioxid and the urine may contain a trace of albumin. At the eighteen hour period, the lipoid is still further increased in amount. The nonprotein nitrogen and urea nitrogen of the blood are increased, the phthalein is further decreased, the carbon dioxid is lowered and the urine contains albumin and an occasional cast. At the twenty-four hour period the function of the kidney is further depressed. This depression increases with regularity up to from seventy-two to ninety-six hours (following a 4 mg. injection into a No. 4 rabbit), at which time the phthalein may be as low as 10 per cent., the nonprotein nitrogen and urea nitrogen as high as 250 and 111 mg. per hundred cubic centimeters of blood, respectively, and the carbon dioxid 17.7 per cent. by volume. The urine now contains numerous hyaline and granular casts, often acetone, diacetic acid and a reducing substance. At the time when the kidney is carrying on its work with greatest difficulty, the lipoid material (as determined

by extraction), is lower than at any other time. Further degenerative processes have already been suggested as responsible for this. Following a single subcutaneous injection of 4 mg. of uranium nitrate the kidney function returns to normal within from twelve to fifteen days. The lipoid content, however, was still well below its normal level at fifteen days.

The protective action of sodium carbonate solution in uranium intoxication has been demonstrated by MacNider. He believes that the toxicity of the metal is associated with its ability to produce organic acids and that the carbonate lessens the toxicity by delaying and lessen-

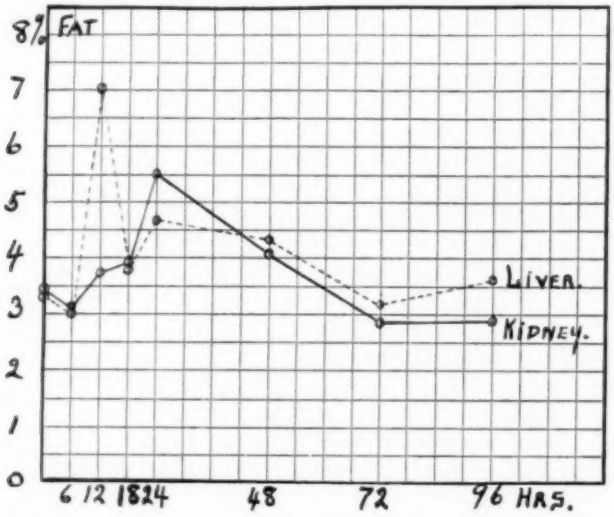

Chart 3.—The lipoid changes in the kidney and liver at different periods, following the onset of an acute nephritis. The nephritis was induced by uranium nitrate with a protecting dose of sodium carbonate at the time of injection of the uranium.

ing the formation of these acids. In the series of animals in which we gave sodium carbonate at the time of the uranium intoxication this protective action was well demonstrated. The depression of the kidney function was materially delayed. The nonprotein nitrogen, the urea nitrogen and the carbon dioxid of the blood were little disturbed for the first forty-eight hours of the experiments. The phthalein output was somewhat reduced and the urine contained traces of albumin. At the seventy-two and ninety-six hour periods, however, functional disturbance was very evident. The alterations in the amounts of extractable lipoid material in both kidney and liver, nevertheless follow curves quite

comparable with the groups of animals in which no protecting carbonate solution was given. The maximum amounts of extractable material were obtained at the twenty-four hour period, the minimum amounts at the seventy-two hour period, and at the end of ninety-six hours a slight increase in the amount of lipoid had occurred. Thus, while the toxic action of the uranium was definitely delayed, had larger amounts of carbonate solution been used, the early minor disturbance and the late marked kidney disturbance might have been avoided and lipoid change in the kidney and liver might not have occurred.

As a further means of studying the relationship of the lipoid content of the kidney to its functional response, we repeated our experiments on a group of animals in which a subacute nephritis had been established

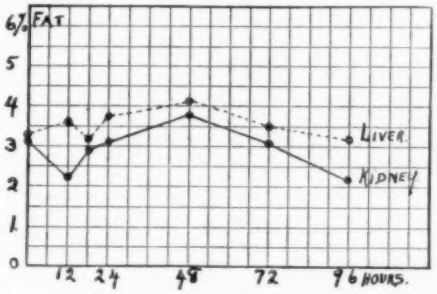

Chart 4.—The percentage of lipoid in the kidney and liver at different intervals, following the onset of an exacerbation of nephritis in kidneys already the seat of a chronic nephritis.

by repeated uranium intoxications. As a result of this nephritis the functional response was lessened. The final injection of uranium did not further materially decrease the function for the reason that an animal develops a tolerance toward the poisoning. Likewise, there was no acidosis as determined by the carbon dioxid of the blood serum. The curves plotting the amounts of extractable lipoid varied from those previously obtained. There was not such a marked variation in the amount of lipoid, the maximum amount was reached a little later (forty-eight hours), and the decrease at the seventy-two hour period was less. In short, in this group of animals in which a subacute nephritis had been established, a final intoxication not sufficiently large to materially increase the degree of nephritis, failed to materially disturb the lipoid content of both kidney and liver. The variation of the lipoid content again maintained a definite relation to the functional response.

The increase of stainable lipoid material at the six hour period was in a majority of instances more pronounced in the liver. By the extraction method there was a greater increase in the amount of lipoid in the

liver, as compared with the kidney, in three of the four series of experiments. The functional response of the liver, could it have been determined as satisfactorily as the response of the kidney, would presumably have shown a diminution.

SUMMARY

Our study is concerned with the question of a possible relationship between the amount of lipoid material in the kidney in acute nephritis and its ability to function.

We have estimated the total amount of lipoid material in the kidney and in the liver by two methods: (1) by the use of Herxheimer's fat staining technic; (2) by chemical extraction in a Soxhlet apparatus.

In a group of normal animals, the average lipoid content of the kidney was 3.43 per cent. and of the liver 3.42 per cent.

The kidneys of these control animals did not contain stainable lipoid material. The livers contained fine dustlike particles of lipoid in the cells in the periphery of the lobules.

An acute nephritis was established in four groups of animals by the subcutaneous injection of uranium nitrate.

The functional response of the kidney in each of these animals was evaluated by a chemical and microscopic examination of the urine, a phthalein determination and readings of the nonprotein nitrogen, urea nitrogen and carbon dioxid of the blood. The amount of stainable and extractable lipoid material in the kidney and liver was determined at stated periods from the time of onset of the nephritis.

In these groups, an increase in the amount of extractable lipoid preceded any alteration in the functional response of the kidney. A maximum increase of lipoid occurred within twenty-four hours, and was followed by a decrease which persisted for as long as fifteen days.

One group of animals was given protective doses of sodium carbonate at the time of injection with uranium nitrate. The decrease in the functional response of the kidney was delayed, but the protective action of the carbonate solution was not sufficient to prevent lipoid changes in the kidney and liver or to prevent a marked decrease in the kidney function during the latter days of the experiments.

In a fourth group of animals in which a well developed subacute nephritis was established by weekly injections of uranium nitrate, the functional response of the kidney was little altered by a final intoxication with the metal, and the amount of extractable lipoid material was likewise little altered.

CONCLUSIONS

An alteration in the amount of stainable and extractable lipoid material in the kidney precedes any alteration in the functional response of this organ in acute experimental nephritis.

From our data, a definite relation was found to exist between the lipoid changes in the kidney and the ability of this organ to function. This relationship continued under a variety of experimental conditions.

A close relationship exists between the degree of fatty change in the kidney and in the liver in experimental nephritis.

The amount of extractable lipoid material in the liver is somewhat greater than that in the kidney under the conditions of our experiments, but curves of these changes are comparable.

Chemical extraction of lipoid material is a more accurate method of determining lipoid changes than the microscopic study of stained sections.

Microscopic evidence of the toxic effect of uranium nitrate occurs in the liver earlier than in the kidney.

In the instances in which lipoid changes were lessened or inhibited, the ability of the kidney to function was less disturbed.

HEMOGLOBIN CONTENT OF THE RED BLOOD CELLS IN RELATION TO THEIR SURFACE AREA*

PRELIMINARY REPORT

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Hemoglobin estimations have for years been used for diagnostic and prognostic purposes, and have also played a part in the investigation of research problems in both medicine and physiology. Under various clinical and experimental conditions, wide variations in the hemoglobin content of the blood have been noted and numerous suggestions have been made to explain this. They are too numerous even to refer to here. If we take into consideration the phenomena recorded in this communication, it becomes obvious that inferences drawn from the hemoglobin variations are liable to be incorrect.

It is not generally recognized that, under ordinary conditions of life, variations of the hemoglobin content of the blood, even to the extent of 30 per cent., may and do frequently occur in the same person during the same day. That such variations do occur was brought to the attention of one of us (R.) some time ago by Dr. A. H. Gordon, attending physician to the Montreal General Hospital. Observations were then being made on the blood of a patient suffering from pernicious anemia. Attention was drawn to the fact that the results of the hemoglobin determination made on this patient one particular afternoon showed a wide discrepancy from that made during the forenoon of the same day. Repeated observations made thereafter on the same person gave very irregular results.

A careful search of the literature proved that records of this phenomenon are very scanty.[1] Because of this, observations were made on a series of twenty apparently normal persons with this special point in view. The routine habits of the individual as to diet, time of meals, etc., were not disturbed. Hemoglobin estimations were made every two hours during the day from 8.00 a. m. until 6.00 p. m. The blood was obtained by venous puncture and the hemoglobin calculated from the oxygen carrying capacity, by means of the formula of Van Slyke. The

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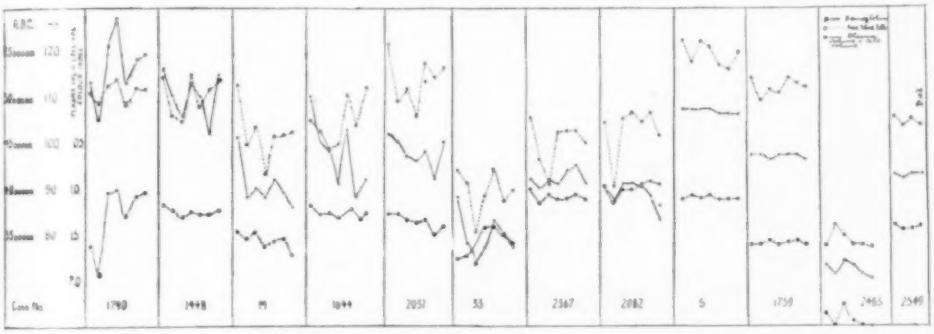
1. Dreyer, G.; Bazett, H. C., and Pierce, H. F.: Lancet **2**:588 (Sept. 18) 1920.

results of these observations have already been reported.[2] It appears to be an established fact that marked variations, even to the extent of 30 per cent. in the hemoglobin content of the blood, may occur in the same person in the same day.

Since then, further studies have been made under varying conditions, and an attempt was made to determine the possible factors governing these variations. Diets, consisting of constant intake of solids and fluids, and meals given at definite periods of the day failed to alter the variation curves. Rest in bed, with the minimum essential muscular movements, and the presence or absence of fever seemed to bear no relation to them. One observation which is of interest is: that in practically all patients with advanced heart failure, a marked fixation in the hemoglobin curves was noted.



Hemoglobin, cell count, blood volume time curve.

The principal object of this paper is to record a phenomenon which does not appear to have been hitherto reported. That is the relation between the surface area of the red blood cells and their hemoglobin content. Following the first twenty observations, which were made on hemoglobin content only, an attempt was made to co-ordinate the hemoglobin data with those of cell counts, color indexes and proportion of plasma to cell volume. In Table 1 are found the combined data and these are graphically recorded in the chart. For brevity, only type cases are shown representing the different types of curves noted.

TECHNIC

All cell counts were made by the same person (S), and represent the average of three readings, all varying within 100,000. The hemoglobin determinations were made by the Van Slyke (oxygen carrying

2. Rabinowitch, I. M.: J. Lab. & Clin. Med. **9**:120 (Nov.) 1923.

capacity) method. The proportions of plasma and cell volume were obtained by centrifugating all the blood specimens of the same individual, at the same time, in separate glass tubes of equal bore, for thirty minutes at 3,000 revolutions a minute.

RESULTS

The interpretation of the data in cases number 1790 and number 33 do not appear to present any difficulty. Since the percentage of hemo-

TABLE 1.—*The Combined Data of Hemoglobin and Cell Counts.*

Time	Red Blood Cells	Hb.	P/C*	I**	Red Blood Cells	Hb.	P/C	I	Red Blood Cells	Hb.	P/C	I
8 a. m.	5.10	114	1.57	1.11	5.29	117	1.14	1.10	5.19	102	1.42	0.98
10 a. m.	4.96	106	1.88	1.07	4.85	111	1.18	1.14	4.51	89	1.50	0.98
12 m.	5.17	122	1.00	1.18	4.79	106	1.25	1.10	4.72	91	1.43	0.96
2 p. m.	5.25	128	0.96	1.22	5.31	114	1.21	1.07	4.21	80	1.57	1.05
4 p. m.	4.96	114	1.25	1.14	4.97	111	1.23	1.11	4.62	93	1.53	1.00
6 p. m.	5.15	119	1.04	1.15	5.12	113	1.22	1.10	4.64	90	1.50	0.97
8 p. m.	5.13	120	1.10	1.16	5.25	116	1.19	1.10	4.68	87	1.66	0.92
			1790				1448				M	
8 a. m.	4.80	111	1.14	1.17	5.61	103	1.23	0.91	4.26	89	1.72	1.04
10 a. m.	4.69	101	1.24	1.07	5.00	101	1.24	1.01	4.21	79	1.69	0.93
12 m.	4.47	99	1.21	1.10	5.13	98	1.30	0.95	3.56	75	1.76	1.05
2 p. m.	4.54	92	1.36	1.01	4.74	97	1.33	1.02	3.97	78	1.39	0.98
4 p. m.	5.09	104	1.16	1.02	5.41	99	1.30	0.91	4.29	84	1.36	0.97
6 p. m.	4.75	89	1.29	0.93	5.28	93	1.47	0.89	3.91	81	1.45	1.03
8 p. m.	5.15	93	1.23	0.90	5.36	101	1.37	0.94	4.04	78	1.56	0.96
			1644				2037				33	
8 a. m.	4.81	93	0.96	0.96	4.77	91	0.95	0.95	5.65	108	1.06	0.95
10 a. m.	4.36	91	1.13	1.04	4.08	88	1.10	1.07	5.41	108	1.04	0.99
12 m.	4.09	93	1.08	1.13	4.81	92	0.97	0.96	5.64	108	1.06	0.95
2 p. m.	4.66	92	1.07	0.98	4.88	91	0.97	0.93	5.56	108	1.04	0.97
4 p. m.	4.09	95	1.06	1.01	4.78	89	0.93	0.96	5.39	107	1.08	0.99
6 p. m.	4.09	96	1.03	1.02	4.86	87	0.89	0.89	5.48	107	1.08	0.97
8 p. m.	4.54	92	1.07	1.01	4.62	84	0.91	0.90	5.52	107	1.08	0.97
			2367				2082				S	
8 a. m.	5.25	97	1.57	0.92	3.42	74	2.30	1.08	4.81	94	1.36	0.98
10 a. m.	5.50	97	1.57	0.88	3.65	72	2.50	0.96	4.72	93	1.41	0.98
12 m.	5.12	96	1.54	0.93	3.52	75	2.22	1.06	4.80	94	1.40	0.99
2 p. m.	5.09	97	1.57	0.95	3.43	74	2.40	1.07	4.75	94	1.39	0.98
4 p. m.	5.25	97	1.55	0.92	3.41	72	2.60	1.05			Died	
6 p. m.	5.19	98	1.54	0.94	3.40	71	2.64	1.04				
8 p. m.	5.15	97	1.57	0.94								
			1759				2483				2549	

* P/C = plasma volume ÷ cell volume. ** I = color index.

globin varied practically inversely as the proportion of plasma to cell volume, the variations in these cases appear to be a function of the dilution of the blood. This also appears to explain the marked fixation of the curves in the last four cases, number S, number 1759, number 2483 and number 2549. All of these were patients with advanced heart failure. The fixation here may be attributed to the s'owing of the circulation of the body fluids. In the remainder of the cases, however, there is one feature noted, common to all, namely: in spite of the marked variations, both in the cell count and hemoglobin content, there was a

fixation in the proportion of plasma to cell volume. This appears to be clinical significance. A tentative explanation of this phenomenon is suggested.

Since two different specimens of blood, of equal volume, present the same proportions of plasma to cell volume, and since one contains more cells per cubic millimeter than the other, it appears reasonable to assume that the cells of the latter must be of small dimensions. Such a phenomenon, variations in the size of the cells, is generally recognized. The possible variations due to the difficulties met with in hematocrit determinations do not explain the wide discrepancies noted. This decrease in the size of the cell does not, however, explain the presence of the variations in the hemoglobin if we accept the prevalent view that the hemoglobin is contained within the cell. It is obvious that the smaller the cells, with a corresponding increase in number for a given volume of fluid, the greater will be the total cell surface. For this reason it is suggested that the hemoglobin is not contained within the

TABLE 2.—*The Law of Hemoglobin Distribution*

	Hb. Content per 100 C.c. Blood	Red Blood Cells per Mm. in Millions	Average of Single Cell in Gm.	Surface of One Blood Cell in μ^2	Average Hb. Content per μ^2 Surface in 10^{-14} Gm.
Rabbit.....	11.9	5.86	20 by 10^{-12}	68.4	27
Goat.....	10.9	13.94	8 by 10^{-12}	25.1	29

cell, but is distributed on the surface. This appears to be the rational explanation of the observations made in the cases recorded. This view, if correct, opens a new problem as to the structure and composition of the red blood cells. Of interest to note here are the recent observations of two independent workers, Bürker,[3] and Brinkman and Szent-Györgyi.[4] Burker demonstrated a law, that the corpuscular amount of hemoglobin is proportional to the cell surface. Taking as an example cells of different size (rabbit and goat) the law "Haemoglobinverteilungsgesetz" is demonstrated (Table 1).

More recently, the series of experiments by Brinkman and Szent-Györgyi on the electrical conductivity and refractive indexes of partially and totally hemolyzed blood, further strengthen the view that the hemoglobin is not contained within the cell but is distributed about the surface.

These observations appear to be of clinical interest. If the percentage of hemoglobin is a function of cell surface and is dependent on the

3 Bürker, K.: Arch. f. d. ges. Physiol. **195**:516, 1922; Nature **3**:845 (June 23) 1923, abstr., by E. Gorter.

4. Brinkman, R., and Zzent-Györgyi, A.: J. Physiol. **58**:204 (Dec.) 1923.

adsorptive capacity of the stroma of the cells, the importance of a wider application of physicochemical methods in the study of the blood in disease is obvious. These observations are not being extended to the various forms of anemia.

THE EFFECT OF CHOLECYSTECTOMY ON GASTRIC SECRETION *

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It is generally stated that disease of the gallbladder is associated with changes in gastric secretion. Most observers (Holweg,[1] Rohde,[2] Leva[3] and Glaser,[4] and recently Gatewood[5]) have found that hypoacidity and anacidity are present in cases of cholelithiasis and that similar findings are present after cholecystectomy. Other observers,[6] however, have stated that hyperacidity and hypersecretion occur in cases of cholecystitis and in gallbladder disease associated with biliary retention. Thus Simnitsky[7] found hyperacidity in obstruction of the common duct in man and animals.

These observations, particularly the alleged persistence of change in gastric secretion after cholecystectomy, led us to inquire into the relation of the gallbladder to the gastric secretory mechanism. Besides making a study of the effect of cholecystectomy on gastric secretion, we have studied the effect of bile on gastric secretion and have examined the mucosa of the gallbladder for the presence of a gastric secretin.

PROCEDURE

Pawlow pouches were made on five dogs. Their normal gastric secretory response to a test meal of 250 gm. of hamburger was determined by making from ten to twenty control experiments in each dog prior to cholecystectomy. The procedure of each experiment was to collect the continuous secretion for from one to two hours, then feed the test meal and collect the secretion at hourly intervals for from three to five hours. The secretion was titrated for free and total acidity and the pepsin content was determined by Mette's method. After adequate controls, the gallbladder was removed and the secretory response to

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*From the Hull Physiological Laboratory of the University of Chicago.

1. Holweg: Deutsch. Arch. f. klin. Med. **108**:255, 1912.
2. Rohde, C.: Arch. f. klin. Chir. **115**:727 (March) 1921.
3. Leva: Arch. f. Anat. **132**:490, 1893.
4. Glaser: Wien. Med. Wchnschr. **55**:1430, 1905.
5. Gatewood: Achlorhydria in Gallbladder Disease, J. A. M. A. **81**:904 (Sept. 15) 1923.
6. Griffiths, H. E.: Lancet **1**:265 (Feb. 10) 1923.
7. Simnitsky: Berl. klin. Wchnschr. **38**:1077, 1901.

the test meal was followed daily for seven days, and then at intervals of from three to five days for periods of from three weeks to three months.

The animals were dressed daily, and carefully fed and cared for so as to prevent any of the several factors that cause a depression of gastric secretion from entering.

In our experiments on the effect of bile on gastric secretion, we gave from 25 to 50 c.c. of bile obtained from the gallbladders of normal dogs to dogs prepared by the Pawlow pouch method by stomach tube and observed its effect on the secretion of the pouch.

We also applied bile to the intestinal mucosa of a dog prepared with a Thiry's fistula of the jejunum and a gastrostomy, in order to ascertain the effect of bile on the gastric secretion when in the intestine.

In order to ascertain whether or not a gastric secretin was present in the gallbladder mucosa, we obtained 350 gm. of freshly killed hogs' gallbladder and extracted it according to the method of Keeton and Koch,[8] and so diluted the extract that 1 c.c. was equivalent to the amount of 10 gm. of gallbladder. This was injected subcutaneously into the dogs prepared by the Pawlow pouch method in 3 c.c. doses, to test for the presence of a gastric secretin.

RESULTS

Dogs 1 and 2 were studied for twenty-five and twenty-six days, respectively, following cholecystectomy. Dogs 3 and 4 were studied for eighty-seven and 113 days, respectively, after cholecystectomy. Dog 5 died of multiple liver abscesses on the seventh day after cholecystectomy. This animal showed an achylia during the seven day period.

Our results on the four dogs are shown in a condensed form in Tables 1 and 2. It will be seen from these tables that three of the four dogs showed either an achylia or a hyposecretion for from three to eight days after cholecystectomy, the other dog secreting normally on the second day after. None of the animals showed an achylia or even a hyposecretion after the immediate effects of the operation had disappeared. On the contrary, they secreted normally (Dog 3) or greater than normally (Dogs 1, 2 and 4). This hypersecretion is especially evident in Dog 4. It first appeared and was very evident on the day that the animal first ate normally, following the postoperative hyposecretion or achylia, which was associated with anorexia.

Necropsy on Dogs 1, 2, 3 and 4 showed the common bile duct to be slightly dilated, measuring 6 mm., 5 mm., 6 mm. and 6 mm., respectively, in diameter when collapsed. Fibrous adhesions were present at the site of operation in Dog 2, but the other dogs were free from adhesions.

8. Keeton & Koch: Am. J. Physiol. **37**:481, 1915.

We have also observed that two of these cholecystectomized dogs respond normally to gastrin, histamin and other known gastric excitants.

Bile, when given in 50 c.c. amounts by stomach tube to dogs prepared by the Pawlow pouch method, definitely stimulates gastric secretion. This is especially true if the glands are in tone, i. e., secreting free acid, at the time the bile is given (Table 3).

Our results on the application of bile to the intestine (Table 3) show that the stimulating action of bile comes chiefly, if not entirely, from its action in the intestine.

TABLE 1.—*Effect of Cholecystectomy on Gastric Secretion on Dogs Prepared by Pawlow Pouch Method*

Procedure	Amount of Secretion in C.c.			Free Acidity			Total Acidity			Average Pepsin in Mm.
	Minimum	Maximum	Average	Minimum	Maximum	Average	Minimum	Maximum	Average	
Dog 1										
Before cholecystectomy...	7	55	30	25	110	67	40	104	75	8.0
3 days after.....			3			17			25	8.0
5 days after.....			25			87			100	8.0
Next 3 weeks after.....	24	35	30	70	110	88	87	126	105	8.0
Dog 2*										
Before cholecystectomy...	6	21	12	33	57	45	52	80	67	8.0
1st 3 days after.....	achylia									
4 days after.....			4			22			35	
8 days after.....			24			99			108	8.0
Next 3 weeks.....	5	42	18	20	112	50	50	120	67	4.2

* Adhesions found at necropsy. Data presented are the secretions collected for three hours after a test meal.

TABLE 2.—*The Effect of Cholecystectomy on Gastric Secretion on Dogs Prepared by the Pawlow Pouch Method*

Procedure	Amount of Secretion in C.c.			Free Acidity			Total Acidity			Average Pepsin in Mm.
	Minimum	Maximum	Average	Minimum	Maximum	Average	Minimum	Maximum	Average	
Dog 3										
Before cholecystectomy...	18	37	26	44	100	74	57	115	90	6.0
On 2 days after.....			15			55			80	8.0
Next 85 days.....	16	49	28	27	100	60	40	110	80	5.0
Dog 4										
Before cholecystectomy...	6	22	12	10	65	35	33	82	60	9.0
1st 8 days after.....	achylia with poor appetitie									
9th day after.....			51			100			115	6.0
Next 14 days.....	5	16	8	10	60	40	30	80	62	
Next 17 days.....	32	48	42	55	110	85	75	137	115	8.0

Our results (Table 3) on the presence of a gastric secretin in the gallbladder show unquestionably that such a secretin is present, and approximately to the same degree that it is present in the pyloric mucosa.

In connection with our experimental studies, we are able to report the preoperative and postoperative gastric findings in gallbladder disease treated by cholecystectomy. The cases reported are from the service of Dr. Friend, Michael Reese Hospital, and the diagnoses were confirmed by the pathologic report. In reviewing eighty cases of cholecystectomy, we were only able to find five cases in which a gastric analysis

had been done after cholecystectomy. The results are presented briefly in Table 4. In two of the five cases, cholecystectomy caused no change (Cases 4 and 5) in gastric secretion, whereas in two (Cases 1 and 2) there was a reduction in acidity. In Case 3 no preoperative gastric analysis was made, but, at any rate, the cholecystectomy certainly did not cause either subacidity or an achylia as some claim.

TABLE 3.—*Effect of Bile on Gastric Secretion and the Presence of a Gastric Secretin in the Gallbladder on Dogs Prepared by the Pawlow Pouch Method*

		Gastric Secretion			
Procedure	Time o'Clock	Amount, C.c.	Free Acidity	Total Acidity	
Continuous secretion	11-12	6.5	22	35	
Continuous secretion	12-1	5.7	25	50	
50″ bile by stomach tube	1-2	11.0	50	80	
	2-3	10.3	67	90	
	3-4	9.0	50	70	
	4-5	7.5	45	72	
Continuous secretion	12-1	0.7	42	67	
50″ bile by stomach tube	1-2	1.5	62	80	
	2-3	4.6	90	102	
	3-4	2.2	100	110	
	4-5	1.2	80	92	
	5-6	1.2	80	95	
Continuous secretion	1-3	1.5	0	17	
Bile applied to intestine*	3-3:45	22.0	72	105	Latent period 15 min.
	3:45-4:00	10.0	72	105	
	4:00-4:30	1.2	50	75	
Continuous secretion	3-4	3.1	0	12	
3″ gastrin from gallbladder	4-5	23.5	92	110	Subcutaneously
	5-6	26.0	130	137	

* Dog prepared with a Thiry's fistula of the jejunum and a gastrostomy.

TABLE 4.—*The Effect of Cholecystectomy on Gastric Secretion in Five Cases of Cholecystitis in Man*

		Preoperative Gastric Analysis				Postoperative Gastric Analysis			
Case	Diagnosis	Date	Maximum Free Acid	Maximum Total Acid	Date of Operation	Time Since Operation	Maximum Free Acid	Maximum Total Acid	Remarks
1	Chronic cholecystitis	4/20/23	20	32	4/26/23	17 da.	7	10	Subacidity
2	Chronic cholecystitis	3/ 1/19	30	76	4/28/22	17 mo.	23	27	Subacidity
3	Chronic cholecystitis	.....	..	..	.....	2 mo.	62	72	Same as Case 2 before operation
4	Chronic cholecystitis	5/23/22	35	45	5/27/22	22 da.	35	43	No change
5	Cholelithiasis	5/16/21	15	25	5/30/21	2 yr.	17	25	No change

Lactose tea meals with fractional analysis.

COMMENT

Our experimental results show that cholecystectomy in dogs prepared by the Pawlow pouch method does not result in permanent hyposecretion or achylia, which may be present, however, for a short period

after the operation, due, we believe, to the direct effect of the operation and not to the absence of the gallbladder per se. On the other hand, a variable hypersecretion may be observed in some animals. The immediate hypersecretion that occurred in Dog 4 on the ninth day after operation is probably a starvation effect, as it has been observed by Kunde that hypersecretion of gastric juice frequently occurs in dogs prepared by the Pawlow pouch method, following a short or prolonged period of starvation, an observation that has been frequently observed by one of us (Ivy) in the course of other studies on gastric secretion. It is difficult to explain the continued hypersection that we have observed following cholecystectomy. We believe that the explanation involves the solution of two questions: (1) Does the normal gallbladder reflexly inhibit gastric secretion? and (2) how does cholecystectomy influence the discharge of bile into the intestine? We cannot answer these two questions by direct evidence. We do not doubt, however, that some reflex inhibitory mechanism is present, which best accounts for the large percentage of achlorhydrias and hypo-acidities seen in gallstone disease, but it is difficult for us to believe that such an inhibitory mechanism is functioning in the case of the normal gallbladder as it occurred in the dogs used in our experiments.

It is commonly assumed that the removal of the gallbladder causes a more continuous flow of bile into the intestine. This assumption is questioned by Rost,[9] who reports that bile is not always discharged continuously following cholecystectomy. Nevertheless, the explanation of the hypersecretion, when it occurs, is related to the rôle that the bile plays in the digestion of fats and in the causation of the secondary phase of gastric secretion. Our results show that bile itself stimulates gastric secretion, which confirms Sokolov's[10] observations. It has been shown that soaps, fatty acids and glycerol, which are products resulting from the cleavage of fats, stimulate gastric secretion when introduced into the intestine.[11] It is well known that fats inhibit gastric secretion. Thus, it is evident that if bile is made more available by removal of the gallbladder, or any other procedure, gastric secretion will be augmented.

Our results agree in part, but not entirely, with the observations of other experimenters on animals. Holweg[1] observed a diminished acidity, and anacidity, in three out of four dogs, following cholecystectomy. Rohde[2] made similar observations. Dangschat[12] reported that two out of eight dogs showed diminished acidity following cholecystectomy. Rost[9] observed similar results on eleven dogs. Recently Gate-

9. Rost: Mitt. a. d. Grenzgeb. d. Med. u. Chir. **26**:710, 1913.
10. Sokolov: Quoted by Pawlow: The Work of the Digestive Glands, London, C. Griffin and Co., 1910.
11. Ivy, A. C., and McIlvain, G. V.: Am. J. Physiol. **67**:124 (Dec.) 1923.
12. Dangschat: Beit. z. klin. Chir. **128**:605, 1923.

wood [5] reported no change in acidity and secretion in two dogs after cholecystectomy. Since none of these investigators used the Pawlow pouch method on dogs, the ideal preparation for the study of gastric secretion, we are inclined to question the value and accuracy of their observations.

Investigators who have observed a decrease in gastric secretion following cholecystectomy have offered the following explanations: (1) On removal of the gallbladder the flow of bile into the intestine is continuous, as no interdigestive storage of bile in the gallbladder can occur. This continuous presence of bile in the intestine inhibits an alleged "intestinal hormone" from exercising its normal stimulating effect on gastric secretion; (2) Simnitsky [7] reported that hyperacidity and hypersecretion occur in animals after ligation of the common bile duct and in icterus, which he believed was due to an assumed inhibitory action of bile in the intestine on gastric secretion. Rost [9] believed that the hypoacidity was due to a diminished secretion of bile and pancreatic juice. In the light of our observations the first two explanations are false, because bile does not inhibit, but excites gastric secretion. Rost's observation lacks confirmation, and we feel that it should be confirmed, because we cannot understand why cholecystectomy should result in a depression of biliary and pancreatic secretion.

The fact that a gastric secretin is present in the gallbladder just adds one more tissue to the already large list of tissues that contain a gastric secretin. We do not believe the presence of a secretin in the gallbladder has any physiologic significance in light of the observations of Keeton, Luckhardt and Koch,[13] of Ivy and Whitlow,[14] and of Lim.[15] If it did play a rôle, we should have observed a depression of gastric secretion in our dogs prepared by the Pawlow pouch method.

The fact that cholecystectomized dogs respond normally to gastrin, histamin, beta-alanine and other excitants shows definitely that their gastric secretory mechanism is fundamentally intact.

Our series of five cases of cholecystectomy adds to the evidence previously presented by Dangschat [12] and Gatewood [5] that achlorhydria does not follow cholecystectomy as maintained by Rydgaard,[16] and that in the majority of patients it remains unaltered.

We feel that clinical reports in many instances fail to take into consideration normal variations in gastric secretion in man. There being many causes for anacidity and achylia, and the clinician not having a record of the normal secretion prior to the disease of the

13. Keeton, R. W.; Luckhardt, A. B., and Koch, F. C.: Am. J. Physiol. **50**:527 (April) 1920; Ibid. **51**:454 (April) 1920.
14. Ivy, A. C., and Whitlow, J. E.: Am. J. Physiol. **60**:578 (May) 1922.
15. Lim: Quart. J. Exper. Physiol. **13**:79, 1922.
16. Rydgaard, F.: Arch. f. klin. Chir. **115**:511 (March) 1921.

gallbladder, are facts that invalidate conclusions drawn concerning the relation of the gallbladder to the gastric secretory mechanism. A depression of gastric secretion accompanied by cholelithiasis and cholecystitis, or removal of the gallbladder, need not necessarily be related to the failure of function or absence of the gallbladder, but may be due to numerous causes. Gallbladder infection, as is well known, is not limited to the gallbladder, but affects the biliary passages, liver, pancreas and adjoining viscera. Inflammatory reactions and the psychic condition of the patient may account for alteration in gastric curves and analyses. Nutritional, appetite and reflex causes may also be important factors. Alder and Ohly [17] believe that anacidity is a primary disease, and that gallbladder disease is secondary to gastritis. Recently McCarthy [18] has expressed a similar opinion. It is well known that removal of the gallbladder does not prevent subsequent disease of the biliary passages.

Many symptoms, such as pyrosis, diarrhea and constipation, following cholecystectomy have been ascribed to the subsequent achylia. This has led many surgeons to hesitate to perform cholecystectomy and to resort to cholecystotomy. Our observations, however, would lead us to the view that the removal of the gallbladder, per se, is not the cause of the achylia or anacidity when it occurs. The persistence of certain symptoms and clinical findings after cholecystectomy may be due to infection or a disturbance of other associated tissues, such as liver, duodenum and pancreas.

SUMMARY

Cholecystectomy in dogs prepared by the Pawlow pouch method does not cause a depression of gastric secretion. In three out of four dogs a variable degree of hypersecretion resulted. Bile in 50 c.c. amounts stimulates gastric secretion when given by stomach tube or applied to the intestinal mucosa. It is pointed out that bile, through its rôle in the digestion of fats, may have an indirect excitatory action on the gastric secretory mechanism.

A gastric secretin is present in gallbladder tissue, but it is believed to be of no physiologic significance. Changes in gastric secretion associated with gallbladder disease is not due to the breaking down of some hypothetic relation between the gallbladder and the gastric secretory mechanism.

17. Alder and Ohly: Quoted by Schultz, E.: Arch. f. Verdanng. **30**:237, 1922.
18. McCarthy, W. C., Alvarez, et al.: abstr., J. A. M. A. **81**:979 (Sept. 22) 1923.

Book Reviews

LABORATORY DIAGNOSIS OF SYPHILIS. By HIDEYO NOGUCHI. Price $7.50. Pp. 392, with 59 illustrations. New York: Paul. B. Hoeber, 1923.

Noguchi has presented in this text complete directions for making the important laboratory tests concerned with the diagnosis of syphilis. The first chapters contain detailed discussion of serum hemolysis, and the quantitative relations to be observed with such hemolysis. These facts are presented for the purpose of showing the importance of quantitative procedures in making serum diagnosis of syphilis. Instructions are given for preparing amboceptor and antigens, and for obtaining complement. Noguchi's system of serum diagnosis is described in detail, also Wassermann's technic. A discussion of the value of the serum diagnosis of syphilis is contained in one chapter. Another is concerned with the effect of treatment on this test. Mention is made of the luetin reaction, and its significance in tertiary, and congenital syphilis. A chapter considers examinations of the spinal fluid. In this are mentioned globulin tests and the procedure and significance of the Lange colloidal gold reaction. In the last portion of the text are given instructions for the dark field examination, the morphologic similarities and differences between *Spirochaeta pallida* and other spirochetes, as well as special staining methods for demonstrating spirochetes in slide and fixed tissue preparations.

The text is recommended to those finding this detailed technic a part of their routine work. The clinician will find helpful the chapters dealing with the significance of, and the effect of treatment on, the serum diagnosis in syphilis.

METHODIK DER RONTGENTIEFENTHERAPIE. By DR. ERNEST POHLE and HANS JARRE. Dresden: Theodor Steinkopff, 1923.

A creditable exposition is made of the basic principles of roentgen-ray absorption necessary for the treatment of deep lying malignancy by short wave rays. Filtration tables and absorption diagrams after the general plan of Dessauer are given. Individual chapters are devoted to the physical principles underlying the treatment of carcinoma of the breast, rectum and uterus. Two short chapters deal with the castration dose and with carcinoma of the larynx.

ZUR THERAPIE DES KARZINOMS MIT RONTGENSTRAHLEN. By F. DESSAUER. Paper cover. Price, 40 cents, second edition (monograph). Dresden and Leipzig: Theodor Steinkopff, 1923.

This monograph is the printed form of four lectures. The first discusses the treatment of carcinoma with physical methods, and the possibility of thereby attaining the desired results; the second deals with the electrotechnical basis of deep roentgen-ray therapy; the third with the dispersion and distribution of roentgen rays in the material, and the fourth with the practical application of the physical portion to deep therapy. The monograph is chiefly theoretical, contains very little new or especially instructive and makes no mention of clinical results.

There are two other related monographs in this series, both on a par with the one reviewed in detail.